Leda Dunn Wettre, Esq.
Michael J. Gesualdo, Esq.
ROBINSON, WETTRE & MILLER LLC
One Newark Center, 19th Floor
Newark, New Jersey 07102
Telephone: (973) 690-5400
Facsimile: (973) 466-2760
lwettre@rwmlegal.com

OF COUNSEL:
William G. Gaede III, Esq. (*pro hac vice*)
David L. Larson, Esq. *(pro hac vice)*
Bhanu K. Sadasivan, Esq. (*pro hac vice*)
Shane G. Smith, Esq. *(pro hac vice)*
Daniel K. Greene, Esq. (*pro hac vice*)
McDERMOTT WILL & EMERY LLP
275 Middlefield Road, Suite 100
Menlo Park, CA 94025-4004
Telephone: +1 650 815 7400

Attorneys for Plaintiff Depomed, Inc.

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

DEPOMED, INC., Plaintiff, v. ACTAVIS ELIZABETH LLC et al., Defendant.	No: 3:12-CV-01358 JAP (TJB) **DEPOMED, INC.'S POST-TRIAL PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW** ***PUBLIC VERSION*** **Honorable Joel A. Pisano**

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I. THE PARTIES

A. PLAINTIFF DEPOMED

1. Plaintiff in this action is Depomed Inc. ("Depomed"). Depomed is a corporation organized under the laws of California, with a principal place of business at 7999 Gateway Blvd., Suite 300, Newark, CA 94560. ECF No. 328, p. 10 [Stip. Facts], ¶1.

2. Depomed is the holder of New Drug Application ("NDA") No. 22-544, by which the U.S. Food and Drug Administration ("FDA") first granted approval for extended release tablets containing the active ingredient 1-(aminomethyl)cyclohexaneacetic acid (known as "gabapentin"). ECF No. 328, p. 10 [Stip. Facts], ¶ 2. The gabapentin gastric-retained, controlled-release tablets described in NDA No. 22-544 are sold by Depomed in the United States under the name Gralise® in two dosage strengths (300 and 600 mg). ECF No. 328, p. 10 [Stip. Facts], ¶ 3.

3. Depomed is the owner of United States Patent No. 6,488,962 (the "'962 Patent") entitled "Tablet Shapes To Enhance Gastric Retention of Swellable Controlled-Release Oral Dosage Forms" issued to Depomed as assignee of the inventors on December 3, 2002. ECF No. 328, p. 11 [Stip. Facts], ¶ 7. FDA's publication *Approved Drug Products with Therapeutic Equivalence Evaluations*

(commonly known as the "Orange Book") identifies the expiration date of the '962 patent as June 20, 2020. *Id*.

4. Depomed is the owner of United States Patent No. 6,635,280 (the "'280 Patent") entitled "Extending the Duration of Drug Release Within the Stomach During the Fed Mode" issued to Depomed as assignee of the inventors on October 21, 2003. ECF No. 328, p. 11 [Stip. Facts], ¶ 8. FDA's publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the "Orange Book") identifies the expiration date of the '280 patent as September 19, 2016. *Id*.

5. Depomed is the owner of United States Patent No. 7,438,927 (the "'927 Patent") entitled "Methods of Treatment Using a Gastric Retained Gabapentin Dosage" issued to Depomed as assignee of the inventors on October 21, 2008. ECF No. 328, pp. 11-12 [Stip. Facts], ¶ 9. FDA's publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the "Orange Book") identifies the expiration date of the '927 patent as February 26, 2024. *Id*.

6. Depomed is the owner of United States Patent No. 7,731,989 (the "'989 Patent") entitled "Gastric Retained Gabapentin Dosage Form" issued to Depomed as assignee of the inventors on June 8, 2010. ECF No. 328, p. 11 [Stip. Facts], ¶ 10. FDA's publication *Approved Drug Products with Therapeutic*

Equivalence Evaluations (commonly known as the "Orange Book") identifies the expiration date of the '989 patent as October 25, 2022. *Id*.

7. Depomed is the owner of United States Patent No. 8,192,756 (the "'756 Patent") entitled "Gastric Retained Gabapentin Dosage Form" issued to Depomed as assignee of the inventors on June 5, 2012. ECF No. 328, p. 12 [Stip. Facts], ¶ 11. FDA's publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the "Orange Book") identifies the expiration date of the '756 patent as October 25, 2022. *Id*.

8. Depomed is the owner of United States Patent No. 8,252,332 B2 (the "'332 Patent") entitled "Gastric Retained Gabapentin Dosage Form" issued to Depomed as assignee of the inventors on August 28, 2012. ECF No. 328, p. 12 [Stip. Facts], ¶ 12. FDA's publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the "Orange Book") identifies the expiration date of the '332 Patent as October 25, 2022. *Id*.

9. Depomed is the owner of United States Patent No. 8,333,992 (the "'992 Patent") entitled "Gastric Retained Gabapentin Dosage Form" issued to Depomed as assignee of the inventors on December 18, 2012. ECF 328, p. 13 [Stip. Facts], ¶ 13. FDA's publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the "Orange Book") identifies the expiration date of the '992 patent as October 25, 2022. *Id*.

10. Depomed was formed in 1995 by Dr. John Shell. (Trial Tr. (Anders), 369:14–20.) Depomed's early efforts were focused on research and development around drug delivery technology. (Trial Tr. (Anders), 369:21–23.) Growth of Depomed has occurred primarily through research and development of products on the licensing of those products. (Trial Tr. (Anders), 370:8–10.) Depomed became a publicly traded company in 1997 with only seven employees. (Trial Tr. (Anders), 369:24–370:5.)

11. Depomed has shifted from being a primarily research, development, and drug delivery technology company to a specialty pharmaceutical company largely due to their commercialization of Gralise. (Trial Tr. (Anders), 373:6–10.) Depomed originally had a partner, Solvay Pharmaceuticals, to commercialize, sell, and market Gralise. (Trial Tr. (Anders), 373:16-21.) Depomed would complete clinical trials, assist with the NDA, and provide manufacturing assistance in exchange for license fees, royalties, and milestone payments. (Trial Tr. (Anders), 373:16–25.) Solvay Pharmaceuticals was purchased by Abbott Products (Abbott Laboratories), which resulted in Depomed obtaining the rights back for Gralise and implementing their own launch plan. (Trial Tr. (Anders), 374:7-19.) This entailed building an entire commercial organization including structures for sales, marketing, and medical affairs groups. (Trial Tr. (Anders), 374:14–25.)

12. The commercialization of Gralise resulted in a growth from 80 to 110 employees just before launch, excluding contract sales representatives. (Trial Tr. (Anders), 375:19–25.) A year after it began promoting Gralise, Depomed had grown to 270 employees and has since grown to over 300 employees. (Trial Tr. (Anders), 369:24–370:5; 375:19–376:2.)

B. DEFENDANTS ACTAVIS

13. The defendants in Civil Action No. 12-CV-01358 are Actavis LLC (f/k/a Actavis, Inc.) and Actavis Elizabeth LLC (collectively "Actavis" or "Defendants"). Actavis LLC is a limited liability corporation organized and existing under the laws of the State of Delaware, having a place of business at 60 Columbia Road, Building B, Morristown, New Jersey 07960. ECF No. 328, p. 10 [Stip. Facts], ¶ 4. Actavis Elizabeth LLC is a limited liability company wholly owned by Actavis LLC and organized and existing under the laws of the State of Delaware, having a principal place of business at 200 Elmora Avenue, Elizabeth, New Jersey 07202. ECF No. 328, pp. 10-11 [Stip. Facts], ¶ 5.

C. DISMISSED PARTIES

1. The Dismissed Defendants

14. In addition to Actavis, five other pharmaceutical companies applied to the FDA for permission to produce a generic version of Gralise. (Trial Tr. (Nicholson), 1088:7-17.)

a. Watson

15. Watson Laboratories, Inc. – Florida and Watson Pharma filed ANDA No. 203625 under Section 505(j) of the Federal Food, Drug, and Cosmetic Act ("the Act") seeking FDA approval to commercially manufacture, use, and sell gabapentin extended-release tablets in 300 mg and 600 mg dosage strengths, prior to the expiration of the patents listed in the Orange Book in connection with NDA 22-544. (Complaint For Patent Infringement, Case No. 12-CV-1358, ECF No. 1 ("Complaint 12-CV-1358"), ¶¶ 26-28; Ex. 8 to Complaint, ECF No. 1-8.) Pursuant to 21 U.S.C. § 355(j)(2)(B), Watson sent a Notice Letter to Depomed informing them of Watson's submission of ANDA No. 203625 to the FDA. *Id.*

16. At the time of filing the complaint, Watson Laboratories, Inc. – Florida was a corporation organized and existing under the laws of the State of Florida and Watson Pharma, Inc. was organized and existing under the laws of Delaware. (Complaint 12-CV-1358 ¶¶ 4-6.) Both companies were wholly owned subsidiaries of Watson Pharmaceuticals, Inc. organized and existing under the laws of the State of Nevada. *Id.* All three companies shall be referred to collectively as "Watson."

17. On March 2, 2012, Depomed filed a Complaint For Patent Infringement in case No. 12-CV-1358 which included Watson as a Defendant and alleged that Watson's filing of its ANDA relating to its 300 and 600 mg strength

gabapentin dosage forms infringed the '475, '962, '280, '340, '927, and '989 Patents under 35 U.S.C. § 271(e)(2)(A) and § 271(a), (b), and (c). (Complaint 12-CV-1358, ¶¶ 39-45, 60-66, 81-87, 102-108, 123-129, 144-150.) On August 10, 2012, Depomed amended its complaint to assert U.S. Patent No. 8,192,756 and remove Watson Pharma, Inc. and Watson Pharmaceuticals, Inc. as defendants. (2nd Amended Complaint For Patent Infringement, Case No. 12-CV-1358, ECF No. 79 ("2nd Complaint 12-CV-1358").) On September 28, 2012, Depomed further amended its complaint to assert U.S. Patent No. 8,252,332. (3rd Amended Complaint For Patent Infringement, Case No. 12-CV-1358, ECF No. 101 ("3rd Complaint 12-CV-1358").)

18. On December 21, 2012, the Court entered a stipulated order of dismissal in Civil Action 12-CV-1358 for Watson. ECF No. 133 [Stipulation and Order of Dismissal Without Prejudice as to Watson]. As a result of this order, Watson was dismissed as a party to this litigation. *Id*. Under the terms of the Stipulation, Watson withdrew its ANDA 203625. *Id*.

b. Incepta

19. Incepta Pharmaceuticals Co and Abon Pharmaceuticals, LLC filed ANDA No. 203643 under Section 505(j) of the Act seeking FDA approval to commercially manufacture, use, and sell gabapentin extended-release tablets in 300 mg and 600 mg dosage strengths, prior to the expiration of the patents listed in the

Orange Book in connection with NDA 22-544. (Complaint 12-CV-1358, ¶¶ 29-31; Ex. 9 to Complaint 12-CV-1358, ECF No. 1-9.) Pursuant to 21 U.S.C. § 355(j)(2)(B), Incepta sent a Notice Letter to Depomed informing them of Incepta's submission of ANDA No. 203643 to the FDA. *Id.*

20. Incepta Pharmaceuticals Co. Ltd. is a Bangladeshi company located at 40 Shahid Tajuddin Ahmed Sarani, Tejgaon I/A, Dhaka-1209, Bangladesh. (Complaint 12-CV-1358, ¶ 8.) Abon Pharmaceuticals, LLC is a company organized and existing under the laws of the State of New Jersey, having a principal place of business at 140 Legrand Ave, Northvale, New Jersey 07647. (2nd Complaint 12-CV-1358, ¶ 9.) Both Incepta Pharmaceuticals Co. and Abon Pharmaceuticals, LLC shall be referred to collectively herein as "Incepta."

21. On March 2, 2012, Depomed filed a Complaint For Patent Infringement in case No. 12-CV-1358 which included Incepta Pharmaceuticals Co. Ltd. as a Defendant and alleged that Incepta's filing of its ANDA relating to its 300 and 600 mg strength gabapentin dosage forms infringed the '475, '962, '280, '340, '927, and '989 Patents under 35 U.S.C. § 271(e)(2)(A) and § 271(a), (b), and (c). (Complaint 12-CV-1358, ¶¶ 46-52, 67-73, 88-94, 109-115, 130-136, 151-157.) On August 10, 2012, Depomed amended its complaint to assert U.S. Patent No. 8,192,756 and add Abon Pharmaceuticals, LLC as a defendant. (2nd Complaint 12-CV-1358.) On September 28, 2012, Depomed further amended its

complaint to assert U.S. Patent No. 8,252,332. (3rd Complaint 12-CV-1358.) On March 6, 2013, Depomed again amended its complaint to assert U.S. Patent No. 8,333,992. (4th Amended Complaint For Patent Infringement, Case No. 12-CV-1358, ECF No. 151.)

22. On April 11, 2014, Incepta entered into a settlement agreement with Depomed in which Incepta agreed not to commercially sell its proposed ANDA No. 203643 products until such day permitted by the settlement and license agreement. ECF No. 358-1 [(Proposed) Consent Injunction and Dismissal Order].

c. Impax

23. Impax Laboratories, Inc. ("Impax") filed ANDA No. 203666 under Section 505(j) of the Act seeking FDA approval to commercially manufacture, use, and sell gabapentin extended-release tablets in 300 mg and 600 mg dosage strengths, prior to the expiration of the patents listed in the Orange Book in connection with NDA 22-544. (Complaint For Patent Infringement, Case No. 12-CV-2154, ECF No. 1 ("Complaint 12-CV-2154") ¶¶ 26-28; Ex. 7 to Complaint 12-CV-2154, ECF No. 1-7.) Pursuant to 21 U.S.C. § 355(j)(2)(B), Impax sent a Notice Letter to Depomed informing them of Impax's submission of ANDA No. 203666 to the FDA. *Id*.

24. At the time of filing the complaint, Impax was a corporation organized and existing under the laws of the State of Delaware. (Complaint 12-CV-2154, ¶ 2.)

25. On April 10, 2012, Depomed filed a complaint against Impax, alleging that Impax's filing of its ANDAs relating to its 300 and 600 mg strength gabapentin dosage forms infringed the '475, '962, '280, '340, '927, and '989 Patents under 35 U.S.C. § 271(e)(2)(A) and § 271(a), (b), and (c). (Complaint 12-CV-2154, ¶¶ 32-38, 46-52, 60-66, 74-80, 88-94, 102-108.) On August 8, 2012, Depomed amended its complaint to assert U.S. Patent No. 8,192,756. (1st Amended Complaint For Patent Infringement, Case No. 12-CV-2154, ECF No. 49 ("1st Complaint 12-CV-2154").) On September 28, 2012, Depomed further amended its complaint to assert U.S. Patent No. 8,252,332. (2nd Amended Complaint For Patent Infringement, Case No. 12-CV-2154 ECF No. 69 ("2nd Complaint 12-CV-2154"))

26. On November 13, 2012, the Court entered a stipulated order of dismissal in Civil Action 12-CV-2154 for Impax. 12-CV-2154 ECF 78 [Stipulation and Order of Dismissal as to Impax]. As a result of this order, Impax was dismissed as a party to this litigation. Under the terms of the Stipulation, Impax withdrew its ANDA 203666. *Id*.

d. Par

27. Par Pharmaceutical Companies, Inc. ("Par") filed ANDA No. 203757 under Section 505(j) of the Act seeking FDA approval to commercially manufacture, use, and sell gabapentin extended-release tablets in 300 mg and 600 mg dosage strengths, prior to the expiration of the patents listed in the Orange Book in connection with NDA 22-544. (Complaint 12-CV-2154 ¶¶ 29-31; 12-CV-2154 ECF No. 1-8.) Pursuant to 21 U.S.C. § 355(j)(2)(B), Par sent a Notice Letter to Depomed informing them of Par's submission of ANDA No. 203757 to the FDA. *Id*.

28. At the time of filing the complaint, Par Pharmaceutical Companies, Inc. wholly owned Par Pharmaceutical, Inc. (Collectively "Par") with both corporations organized and existing under the laws of the State of Delaware. (Complaint 12-CV-2154 ¶¶ 3-4.)

29. On April 10, 2012, Depomed filed a complaint against Par, alleging that Par's filing of its ANDAs relating to its 300 and 600 mg strength gabapentin dosage forms infringed the '475, '962, '280, '340, '927, and '989 Patents under 35 U.S.C. § 271(e)(2)(A) and § 271(a), (b), and (c). (Complaint 12-CV-2154 ¶¶ 39-45, 53-59, 67-73, 81-87, 95-101, 109-115.) On August 8, 2012, Depomed amended its complaint to assert U.S. Patent No. 8,192,756. (1st Complaint 12-CV-

2154.) On September 28, 2012, Depomed further amended its complaint to assert U.S. Patent No. 8,252,332. (2nd Complaint 12-CV-2154.)

30. On December 17, 2012, the Court entered a stipulated order of dismissal in Civil Action 12-CV-2154 for Par. 12-CV-2154 ECF No. 82 [Stipulation and Order of Dismissal as to Defendants Par]. As a result of this order, Par was dismissed as a party to this litigation. *Id*. Under the terms of the Stipulation, Par amended its ANDA 203757 to state a certification under 21 U.S.C. §355(j)(2)(A)(vii)(III) with respect to the patents asserted against them and would no longer seek approval of its ANDA 203757 prior to the expiration of the patents asserted against them at time of the dismissal. *Id*.

e. Zydus

31. Zydus Pharmaceuticals (USA), Inc. filed ANDA No. 203934 under Section 505(j) of the Act seeking FDA approval to commercially manufacture, use, and sell gabapentin extended-release tablets in 300 mg and 600 mg dosage strengths, prior to the expiration of the patents listed in the Orange Book in connection with NDA 22-544. (Complaint For Patent Infringement, Case No. 12-CV-2813 ECF No. 1 ("Complaint 12-CV-2813") ¶¶ 23-25, 12-CV-2813 ECF No. 1-2 [Ex. 7 to Complaint 12-CV-2813]; 12-CV-2813 ECF No. 8-1 [Ex. 8 to 1st Amended Complaint For Patent Infringement, Case No. 12-CV-2813].) Pursuant

to 21 U.S.C. § 355(j)(2)(B), Zydus sent a Notice Letter to Depomed informing them of Zydus's submission of ANDA No. 203934 to the FDA. *Id*.

32. The defendants in Civil Action No. 12-CV-2813 were Zydus Pharmaceuticals (USA), Inc. and Cadila Healthcare Limited. (Complaint 12-CV-2813, ¶¶ 2-5.) Zydus USA is a corporation organized and existing under the laws of the State of New Jersey with its principal place of business at 73 Route 31 N., Pennington, New Jersey 08534. *Id*. Cadila Healthcare Limited is an Indian company located at Zydus Tower, Satellite Cross Roads, Ahmedabad – 380015, Gujarat, India. *Id*. Both Zydus Pharmaceuticals (USA), Inc. and Cadila Healthcare Limited shall be referred to herein collectively as "Zydus."

33. On May 9, 2012, Depomed filed a complaint against Zydus, alleging that Zydus's filing of its ANDA No. 203934 relating to its 300 and 600 mg strength gabapentin dosage form infringed the '475, '962, '280, '340, '927, and '989 Patents under 35 U.S.C. § 271(e)(2)(A) and § 271(a), (b), and (c). (Complaint 12-CV-2813 ¶¶ 26-67.) On August 8, 2012, and Depomed amended its complaint to assert U.S. Patent No. 8,192,756. (2nd Amended Complaint For Patent Infringement, Case No. 12-CV-2813, ECF No. 40.) On September 28, 2012, Depomed amended its complaint to assert U.S. Patent No. 8,252,332. (3rd Amended Complaint For Patent Infringement, Case No. 12-CV-2813, ECF No. 54.) On March 6, 2013, Depomed again amended its complaint to assert U.S.

Patent No. 8,333,992. (4th Amended Complaint For Patent Infringement, Case No. 12-CV-2813, ECF No. 78.)

34. On April 11, 2014, Zydus entered into a settlement agreement with Depomed in which Zydus agreed to be enjoined from manufacturing, using, offering to sell or selling within the U.S. and territories its proposed ANDA No. 203643 products until such time as permitted by the Settlement and License Agreement. (*See* Consent Injunction and Dismissal Order, Case No. 12-CV-2813, ECF No. 174.) The case against Zydus was dismissed June 9, 2014. *Id.*

II. NATURE OF THE ACTION

35. The present action is for patent infringement under 35 U.S.C. §271(e)(2)(A) and the Hatch-Waxman Act, codified in part at 21 U.S.C. § 355(j). ECF No. 328, p. 14 [Stip. Facts], ¶ 23.) The Patent Act makes it an act of patent infringement to submit an Abbreviated New Drug Application ("ANDA") seeking FDA approval for a drug prior to the expiration of a patent claiming that drug or the use of that drug. (35 U.S.C. § 271(e)(2)(A).)

36. Actavis submitted an Abbreviated New Drug Application ("ANDA") No. 203611 with the FDA seeking approval to commercially manufacture, use, and sell generic gabapentin extended-release tablets in dosage strengths of 300 mg and 600 mg (the "Actavis ANDA product") prior to the expiration of the patents listed in the Orange Book in connection with NDA 22-544 (the "patents-in-suit"). ECF

No. 328, p. 13 [Stip. Facts], ¶ 14. Pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV Certification"), Actavis' ANDA No. 203611 included a certification with respect to the patents listed in the Orange Book in connection with NDA 22-544 that, in the opinion of the defendants, the claims of the patents-in-suit will not be infringed by the product that is the subject of the ANDA or are invalid. ECF No. 328, p. 13 [Stip. Facts], ¶ 15.

37. Pursuant to 21 U.S.C. § 355(j)(2)(B), Actavis sent Depomed four letters advising Depomed that defendant had submitted its ANDA and that the ANDA included a Paragraph IV Certification with respect to the patents-in-suit ("Notice Letter"). ECF No. 328, p. 13 [Stip. Facts], ¶ 16. Actavis sent Notice Letters dated January 19, 2012 (referring to the '475, '962, '280, '927, '340 and '989 Patents), June 26, 2012 (to include the '756 Patent), November 16, 2012 (to include the '332 Patent), and February 19, 2013 (to include the '992 Patent). ECF No. 328, pp. 13-14 [Stip. Facts], ¶¶ 16, 18, 20, and 22.

38. On March 2, 2012, Depomed filed a complaint against Actavis alleging that Actavis's filing of its ANDA relating to its 300 and 600 mg strength gabapentin dosage forms infringed the '475, '962, '280, '340, '927, and '989 Patents under 35 U.S.C. § 271(e)(2)(A) and requesting declaratory relief under § 271(a), (b), and (c). ECF No. 328, pp. 14-15 [Stip. Facts], ¶ 24. On August 10, 2012, Depomed amended its complaint to assert U.S. Patent No. 8,192,756 on the

same grounds. ECF No. 328, p. 15 [Stip. Facts], ¶ 28. On September 28, 2012, Depomed further amended its complaint to assert U.S. Patent No. 8,252,332 on the same grounds. ECF No. 328, p. 15 [Stip. Facts], ¶ 31. On March 6, 2013, Depomed again amended its complaint to assert U.S. Patent No. 8,333,992 on the same grounds. ECF No. 328, p. 16 [Stip. Facts], ¶ 34.

III. WITNESSES PRESENTED AT TRIAL

39. Trial in these actions proceeded as follows. Depomed, in its infringement case-in-chief against Actavis, called five expert witnesses, Dr. Eden Tesfu, Dr. Gary Annunziata, Dr. Hartmut Derendorf, Dr. Robert O. Williams, and Dr. Howard Hopfenberg. In addition, Depomed presented the testimony of three fact witnesses, Mr. Jack Lee Anders, VP of Finance for Depomed Inc., Dr. Radi Hejazi, Formulation Scientist at Actavis Elizabeth, and Dr. Meena Venugopal, former employee at Actavis.

40. In its response case, defendant Actavis called only one expert witness, Dr. David Friend.

41. Defendants then put on their obviousness case-in-chief through two expert witnesses: Dr. Douglas Flanagan and Dr. Michael Mayersohn. Defendants also presented a portion of the deposition of inventor Dr. Eddie Hou by video.

42. In its response case, Depomed called Dr. Howard Bockbrader, Dr. Barry Gidal, Dr. Michelle Brown, Dr. Howard Hopfenberg, Dr. Linda Felton, Dr.

Hartumut Derendorf, and Dr. Sean Nicholson. Depomed also presented the testimony by deposition of Dr. Andrew Johnson, Analytical Scientist for Actavis.

43. Defendants, in rebuttal, called two expert witnesses, Dr. Raymond Sinatra and Dr. Ryan Michael Sullivan.

A. DEPOMED'S WITNESSES

44. Dr. Radi Hejazi is a Formulation Scientist at Actavis Elizabeth. (Trial Tr. (Hejazi), 51:8-13.) Dr. Hejazi testified as to the development of the Actavis ANDA product including the ingredients used and the type of die for casting the tablets. (Trial Tr. (Hejazi), 50-88.)

45. Dr. Eden Tesfu was accepted by the Court as an expert in analytical chemistry. (Trial Tr. (Tesfu), 92:19-22.) Dr. Tesfu a laboratory manager at Evans Analytical Life Sciences where she oversaw swelling and dissolution studies performed on the Defendants' proposed ANDA product and Plaintiff's Gralise® tablet. (Trial Tr. (Tesfu) 89-134.)

46. Dr Gary Annunziata was accepted by the Court as an expert in stomach physiology. (Trial Tr. (Annunziata), 148:12-14.) Dr. Annunziata testified as to the size of the human pylorus under different feeding conditions and the process of stomach digestion and emptying. (Trial Tr. (Annunziata), 141-168, 207-260.)

47. Dr. Robert O. Williams was accepted by the Court as an expert in the field of formulation and pharmaceutical sciences. (Trial Tr. (Williams), 264:4–7.) Dr. Williams testified as to the ingredients and swelling properties of the Actavis proposed ANDA product and Gralise tablets. (Trial Tr. (Williams), 260-309.)

48. Dr. Meena Venugopal is a former employee at Actavis who oversaw bioequivalence studies to support ANDA filings. (Trial Tr. (Venugopal), 310:25-311:5.) Dr. Venugopal testified on the pharmacokinetic studies performed as part of the ANDA 203611 bioequivalence studies. (Trial Tr. (Venugopal), 310-331.)

49. Dr. Hartmut Derendorf was accepted as an expert in the field of pharmacokinetics by the court. (Trial Tr. (Derendorf), 336:5–8.) Dr. Derendorf testified on the pharmacokinetic data from the Actavis ANDA and evidence for gastric retention. (Trial Tr. (Derendorf), 332-367.) Dr. Derendorf also testified as to the non-obviousness of the patents-in-suit in Depomed's response case. (Trial Tr. (Derendorf), 1022-1061.)

50. Mr. Jack Lee Anders is the VP of Finance for Depomed Inc. (Trial Tr. (Anders), 368:9-13.) Mr. Anders testified as to the growth of Depomed due to the development of the Gralise® product. (Trial Tr. (Anders), 368-396.)

51. Dr. Harold Hopfenberg, was accepted by the Court as an expert in polymer science and controlled release dosage forms. (Trial Tr. (Hopfenberg), 437:13-19.) Dr. Hopfenberg testified as to the shape and swelling of the Actavis

ANDA product. (Trial Tr. (Hopfenberg), 431-494.) Dr. Hopfenberg also testified as to the non-obviousness of the '962 Patent in Depomed's response case. (Trial Tr. (Hopfenberg), 931-955.)

52. Dr. Howard Bockbrader was accepted by the Court as an expert in the area of clinical pharmacokinetics and particularly the pharmacokinetics of gabapentin. (Trial Tr. (Bockbrader), 748:8-13.) Dr. Bockbrader testified as to the failure of Warner-Lambert to develop an extended release gabapentin product and its skepticism as to whether a gastric retained gabapentin product could be developed. (Trial Tr. (Bockbrader), 743-777.)

53. Dr. Barry Gidal was accepted by the Court as an expert on gabapentin pharmacokinetics and pharmacodynamics. (Trial Tr. (Gidal), 815:14-816:2.) Dr. Gidal testified as to skepticism on the ability to develop a controlled-release gabapentin tablet. (Trial Tr. (Gidal), 811-865.)

54. Dr. Michelle Brown was accepted by the Court as an expert in the area of treating neuropathic pain. (Trial Tr. (Brown), 869:4-20.) Dr. Brown testified as to the long felt need for a controlled-release gabapentin product and the way that Gralise is prescribed. (Trial Tr. (Brown), 866-893.)

55. Dr. Linda Felton was accepted by the Court as an expert in controlled-release dosage forms. (Trial Tr. (Felton), 959:1-4.) Dr. Felton testified as to the

non-obviousness of a controlled-release gabapentin tablet. (Trial Tr. (Felton), 955-1021.)

56. Dr. Sean Nicholson was accepted by the Court as an expert in the field of economics in healthcare. (Trial Tr. (Nicholson), 1064:5-7.) Dr. Nicholson testified as to the commercial success of the Gralise® product and patents-in-suit. (Trial Tr. (Nicholson), 1061-1099.)

57. Dr. Andrew Johnson is an Analytical Scientist and Project Manager at Actavis Elizabeth. (Trial Tr. (Johnson), 1137:24-1138:8.) Dr. Johnson was involved in the development of the dissolution data for the Actavis ANDA 203611. (Trial Tr. (Johnson), 1137:24-1138:8, 1139:6-10.) Dr. Johnson, by video recorded deposition, testified as to the extraordinary efforts put forth by Actavis to be the first company to file an ANDA to make a generic Gralise® product. (Trial Tr. (Johnson), 1137-1163.)

B. DEFENDANTS' WITNESSES

58. Dr. David Friend was admitted as an expert in the design and development of controlled-release dosage forms, design and development of gastric retained dosage forms, behavior of dosage forms in the stomach during fed mode and the sizes and shapes of oral dosage forms. (Trial Tr. (Friend), 502:3-8, 504:2.) Dr. Friend was not admitted to testify as an expert in pharmacokinetics.

(Trial Tr. (Friend), 502:3-8, 504:2, 541:2-10.) Dr. Friend testified as to the shape and swelling of the Actavis ANDA tablet. (Trial Tr. (Friend), 497-547.)

59. Dr. Sui Yuen "Eddie" Hou is an inventor on the '927, '989, '756, '332, and '992 Patents. Dr. Hou, via video recorded deposition, testified on the individuals involved in developing Gralise®. (Trial Tr. (Hou), 547-549.)

60. Dr. Douglas Flanagan was accepted by the Court as an expert in pharmaceutical formulation, including the design and development of controlled-release dosage forms. (Trial Tr. (Flanagan), 552:10-14.) Dr. Flanagan testified as to the obviousness of the '927, '989, '756, '332, '992 Patents. (Trial Tr. (Flanagan), 549-578, 608-687.)

61. Dr. Michael Mayersohn was accepted by the Court as an expert in drug absorption and pharmacokinetics. (Trial Tr. (Mayersohn), 692:6-10.) Dr. Mayersohn testified as to the obviousness of the '332 and '992 Patents. (Trial Tr. (Mayersohn), 688-742.)

62. Dr. Raymond Sinatra was accepted by the Court as an expert in pain medicine and the prescribing practices of physicians in pain management. (Trial Tr. (Sinatra), 895:21-24.) Dr. Sinatra testified as to clinical trials performed on Gralise. (Trial Tr. (Sinatra), 893-908.)

63. Dr. Ryan Michael Sullivan was accepted by the Court as an expert in the economics of intellectual property as it pertains to pharmaceutical products.

(Trial Tr. (Sullivan), 1165:25-1166:5.) Dr. Sullivan testified as to his evaluation of the commercial success of Gralise. (Trial Tr. (Sullivan), 1164-1201.)

IV. PROPOSED FINDINGS OF FACT – INFRINGEMENT OF THE ASSERTED GABAPENTIN PATENTS

A. THE ASSERTED GABAPENTIN PATENTS

1. The '927 Patent Asserted Claim Nos. 18, 25, 26, 34, 61 and 62

64. The '927 Patent issued from an application (No. 10/280,309) filed in the USPTO on October 25, 2002, naming as inventors Bret Berner, Sui Yuen Eddie Hou, and Gloria M. Gusler ("the '927 patent application"). (JTX003.)

65. The '927 Patent claims priority to an October 25, 2001 provisional application. The '927 Patent expires on February 26, 2024. (JTX011 (DEPOACT0003898).)

66. Six claims, Claims 18, 25, 26, 34, 61, and 62, from the '927 Patent are being asserted against the Actavis ANDA Products.

67. Claims 18, 25, 26, and 61 depend upon claim 17. Claims 34 and 62 are dependent upon Claim 33.

68. Independent Claim 17 of the '927 Patent reads as follows:

> A method of treating neuropathic pain in a mammal comprising administering a therapeutically effective amount of a daily dosage of about 100 mg to about 4800 mg of gabapentin or a pharmaceutically acceptable salt thereof, dispersed in a gastric retained dosage form to the mammal in which a fed mode has been induced, wherein the dosage form comprises a single polymer matrix comprising at least one swellable hydrophilic polymer that swells in a dimensionally

unrestrained manner by imbibing water to increase its size to promote gastric retention of the dosage form in the stomach of the mammal, and wherein upon contact with water, gabapentin is released by diffusion from the dosage form over a period of at least five hours and at least 40 wt% of the gabapentin is retained in the dosage form one hour after administration.

69. Asserted dependent Claim 18 of the '927 Patent reads as follows:

The method of claim 17 wherein the dosage form is administered once-daily.

70. Asserted dependent Claim 25 of the '927 Patent reads as follows:

The method of claim 17 wherein the gastric retained dosage form releases gabapentin to the stomach, duodenum and small intestine.

71. Asserted dependent Claim 26 of the '927 Patent reads as follows:

The method of claim 17 wherein the dosage form provides administration of at least 85 wt % of the gabapentin to be delivered over a period of about 5-12 hours.

72. Asserted dependent Claim 61 of the '927 Patent reads as follows:

The method of claim 17, wherein the mammal is a human.

73. Independent Claim 33 of the '927 Patent reads as follows:

A method of administering a therapeutically effective amount of a daily dosage of about 100 mg to about 4800 mg of gabapentin to a mammal, comprising administering gabapentin or a pharmaceutically acceptable salt thereof, dispersed in a gastric retained dosage form to the mammal in which a fed mode has been induced and wherein the dosage form comprises a single polymer matrix comprising at least one swellable hydrophilic polymer that swells in a dimensionally unrestrained manner by imbibing water to increase its size to promote gastric retention of the dosage form in the stomach of the mammal, and wherein upon contact with water, gabapentin is released by diffusion from the dosage form over a period of at least five hours and

> at least 40 wt % of the gabapentin is retained in the dosage form one hour after administration.

74. Asserted dependent Claim 34 of the '927 Patent reads as follows:

> The method of claim 33 wherein the dosage form is administered once-daily.

75. Asserted dependent Claim 62 of the '927 Patent reads as follows:

76. The method of claim 33, wherein the mammal is a human.

2. The '989 Patent Asserted Claim No. 10

77. The '989 Patent issued from an application (No. 12/239,591) filed in the USPTO on September 26, 2008, naming as inventors Bret Berner, Sui Yuen Eddie Hou, and Gloria M. Gusler ("the '989 patent application"). (JTX004.)

78. The '989 patent claims a priority date to the same provisional application as the '927 Patent and is a continuation application of the application that issued as the '927 Patent. ('989 Patent (JTX004), p. 1.) The '989 Patent expires on October 25, 2022.

79. One claim, Claim 10, from the '989 Patent is being asserted against the ANDA Products and depends from Claim 1.

80. Claim 1 of the '989 Patent reads as follows:

> A dosage form, comprising between about 100 mg to about 4800 mg of gabapentin or pharmaceutically acceptable salt thereof, dispersed in a single polymer matrix comprising at least one swellable hydrophilic polymer that swells unrestrained dimensionally by imbibing water to increase its size to promote gastric retention of the dosage form in a stomach in a fed mode, wherein upon contact with water, gabapentin is released by diffusion from the dosage form over a period of at least

five hours and at least 40 wt % of the gabapentin is retained in the dosage form 1 hour after administration.

81. Asserted dependent Claim 10 of the '989 Patent reads as follows:

The dosage form of claim 1, wherein the gabapentin has a bioavailability greater than or equal to 80% of an equal dose of gabapentin in an immediate release dosage form.

3. The '756 Patent Asserted Claim Nos. 1, 2, 5, 6, 7 and 11

82. The '756 Patent issued from an application (No. 13/111,575) filed in the USPTO on May 19, 2011, naming as inventors Bret Berner, Sui Yuen Eddie Hou, and Gloria M. Gusler ("the '756 patent application"). The '756 Patent issued from a continuation application of the '927 Patent application and claims the same priority date of October 25, 2001. ('756 Patent (JTX005), p. 1.) The '756 Patent expires on October 25, 2022.

83. Six claims, Claims 1, 2, 5, 6, 7, and 11 from the '756 Patent are being asserted against the ANDA Products.

84. Claims 2 and 5 are dependent upon Claim 1. Claims 7 and 11 are dependent upon Claim 6.

85. Asserted independent Claim 1 of the '756 Patent reads as follows:

A dosage form, comprising: comprising from 100 mg to 4800 mg of therapeutically effective amount of gabapentin or pharmaceutically acceptable salt thereof, dispersed in a single matrix wherein the matrix comprises at least one swellable hydrophilic polymer that swells unrestrained dimensionally by imbibing water to increase its size to promote gastric retention of the dosage form in the stomach in a fed mode, wherein upon once-daily or twice-daily ingestion of the dosage form gabapentin is released from the matrix over a period of at least

> five hours wherein at least 40 wt% of the gabapentin is retained in the matrix one hour after administration, and wherein the gabapentin is released at a rate sufficient to achieve a lower maximum plasma concentration (C_{max})compared to an equal dose of gabapentin provided by an immediate release dosage form, and without loss in bioavailability as measured by the area under the curve ($AUC_{infinity}$) as compared to the bioavailability which is achieved from an immediate release dosage form comprising the same dose of gabapentin.

86. The Court has construed "without loss in bioavailability as measured by the area under the curve ($AUC_{infinity}$) as compared to the bioavailability which is achieved from an immediate release dosage form comprising the same dose of gabapentin," as recited in Claims 1 and 6 of the '756 Patent, to mean "bioavailability as measured by the area under the curve ($AUC_{infinity}$) is at least 80% of an equal dose of gabapentin in an immediate release dosage form." ECF 251, pp. 21-22 [Opinion].

87. Asserted dependent Claim 2 of the '756 Patent reads as follows:

> The dosage form of claim 1, wherein the time to reach maximum plasma concentration is longer relative to the time to reach maximum plasma concentration from an immediate release dosage form comprising the dose of gabapentin.

88. Asserted dependent Claim 5 of the '756 Patent reads as follows:

> The dosage form of claim 1, comprising a dose of gabapentin of between about 300-600 mg.

89. Asserted independent Claim 6 of the '756 Patent reads as follows:

> A method of treating a condition responsive to a therapeutic dose of gabapentin, comprising: orally administering once-daily or twice daily a dosage form comprising between about 100 mg to about 4800 mg of gabapentin or pharmaceutically acceptable salt thereof, dispersed in a

> single matrix, wherein the matrix comprises at least one swellable hydrophilic polymer that swells unrestrained dimensionally by imbibing water to increase its size to promote gastric retention of the dosage form in the stomach in a fed mode, wherein upon once-daily or twice daily ingestion of the dosage form gabapentin is released from the matrix over a period of at least five hours wherein at least 40 wt% of the gabapentin is retained in the matrix one hour after administration, and whereby the dosage form releases gabapentin at a rate sufficient to achieve a lower maximum plasma concentration (C_{max}) compared to an equal dose of gabapentin provided by an immediate release dosage form, and without loss in bioavailability as measured by the area under the curve ($AUC_{infinity}$) as compared to the bioavailability which is achieved from an immediate release dosage form comprising the same dose of gabapentin.

90. Asserted dependent Claim 7 of the '756 Patent. Claim 7 reads as follows:

> The method of claim 6, wherein the time to reach maximum plasma concentration is longer relative to the time to reach maximum plasma concentration from an immediate release dosage form comprising the dose of gabapentin.

91. Asserted dependent Claim 11 of the '756 Patent. Claim 11 reads as follows:

> The method of claim 6, wherein the condition is neuropathic pain.

4. The '332 Patent Asserted Claim Nos. 1, 6, 17, 22 and 24

92. The '332 Patent issued from an application (No. 12/749,101) filed in the USPTO on March 29, 2010, naming as inventors Bret Berner, Sui Yuen Eddie Hou, and Gloria M. Gusler ("the '332 patent application"). (JTX006.)

93. The '332 Patent claims a priority date to the same October 25, 2001 provision application as the '927 Patent and issued from a continuation application

of the application that issued as the '927 Patent. ('332 Patent (JTX006), p. 1.) The '332 Patent expires on October 25, 2022.

94. Five claims, Claims 1, 6, 17, 22, and 24, from the '332 Patent are being asserted against the ANDA Products.

95. Claim 6 is dependent upon Claims 5, 4, and 1. Claim 17 is dependent upon Claim 12.

96. Asserted independent Claim 1 of the '332 Patent reads as follows:

> A dosage form, comprising a matrix comprising gabapentin, wherein upon ingestion of the dosage form gabapentin is released from the matrix into the upper gastrointestinal tract over about 5-12 hours at a rate sufficient to achieve a lower maximum plasma concentration than that provided by an immediate release dosage form comprising an equal amount of gabapentin, and bioavailability of gabapentin is at least 80% of that provided by the immediate release dosage form comprising an equal amount of gabapentin as measured by the area under the plasma concentration-time curve, AUC_{inf}.

97. Dependent Claim 4 of the '332 Patent reads as follows:

> The dosage form of claim 1, wherein the matrix is a polymer matrix.

98. Dependent Claim 5 of the '332 Patent reads as follows:

> The dosage form of claim 4, wherein the polymer matrix is comprised of a swellable, hydrophilic polymer.

99. Asserted dependent Claim 6 of the '332 Patent reads as follows:

> The dosage form of claim 5, wherein the gabapentin is released from the polymer matrix by diffusion.

100. Independent Claim 12 of the '332 Patent reads as follows:

A method of treating a condition responsive to a therapeutic dose of gabapentin, comprising: orally administering a dosage form, comprising a matrix comprising gabapentin, wherein upon ingestion of the dosage form gabapentin is released from the matrix into the upper gastrointestinal tract over about 5-12 hours at a rate sufficient to achieve a lower maximum plasma concentration than that provided by an immediate release dosage form comprising an equal amount of gabapentin, and bioavailability of gabapentin is at least 80% of that provided by the immediate release dosage form comprising an equal amount of gabapentin as measured by the area under the plasma concentration-time curve, AUC_{inf}.

101. Asserted dependent Claim 17 of the '332 Patent reads as follows:

The method of claim 12, wherein the condition is neuropathic pain.

102. Asserted independent Claim 22 of the '332 Patent reads as follows:

A dosage form, comprising a matrix comprising gabapentin, wherein upon ingestion of the dosage form gabapentin is released from the matrix into the upper gastrointestinal tract over about 5-12 hours at a rate sufficient to achieve a longer time to the maximum plasma concentration than that provided by an immediate release dosage form comprising an equal amount of gabapentin, and bioavailability of gabapentin is at least 80% of that provided by the immediate release dosage form comprising an equal amount of gabapentin as measured by the area under the plasma concentration-time curve, AUC_{inf}.

103. Asserted independent Claim 24 of the '332 Patent reads as follows:

A method of treating a condition responsive to a therapeutic dose of gabapentin, comprising orally administering a dosage form comprising a matrix comprising gabapentin, wherein gabapentin is released from the matrix into the upper gastrointestinal tract over about 5-12 hours at a rate sufficient to achieve a longer time to the maximum plasma concentration than that provided by an immediate release dosage form comprising an equal amount of gabapentin, and bioavailability of gabapentin is at least 80% of that provided by the immediate release dosage form comprising an equal amount of gabapentin as measured by the area under the plasma concentration-time curve, AUC_{inf}.

5. The '992 Patent Asserted Claim Nos. 1, 5 and 22

104. The '992 Patent issued from an application (No. 13/560,938) filed in the USPTO on July 27, 2012, naming as inventors Bret Berner, Sui Yuen Eddie Hou, and Gloria M. Gusler ("the '992 patent application"). (JTX007.)

105. The '992 Patent claims a priority date to the same October 25, 2001 provisional application as the '927 Patent and issued from a continuation application of the application that issued as the '927 Patent. ('992 Patent (JTX007), p. 1.) The '992 Patent expires on October 25, 2022.

106. Three claims, Claims 1, 5, and 22, from the '992 Patent are being asserted against the ANDA Products.

107. Claim 5 is dependent upon Claims 4 and 1.

108. Asserted independent Claim 1 of the '992 Patent reads as follows:

> A dosage form, comprising: a matrix comprising gabapentin, wherein upon ingestion of the dosage form by a human subject gabapentin is released from the matrix into the upper gastrointestinal tract over about 5-12 hours at a rate sufficient to achieve a lower maximum plasma concentration than that provided by an immediate release dosage form comprising an equal amount of gabapentin, and bioavailability of gabapentin is at least 80% of that provided by the immediate release dosage form comprising an equal amount of gabapentin as measured by the area under the plasma concentration-time curve, AUC_{inf}.

109. Dependent Claim 4 of the '992 Patent reads as follows:

> The dosage form of claim 1, wherein the matrix is a polymer matrix.

110. Asserted dependent Claim 5 of the '992 Patent reads as follows:

The dosage form of claim 4, wherein the polymer matrix is comprised of a swellable, hydrophilic polymer.

111. Asserted independent Claim 22 of the '992 Patent reads as follows:

A method of treating a condition responsive to a therapeutic dose of gabapentin, comprising: orally administering to a human subject a dosage form comprising a matrix comprising gabapentin, wherein gabapentin is released from the matrix into the upper gastrointestinal tract over about 5-12 hours at a rate sufficient to achieve a longer time to the maximum plasma concentration than that provided by an immediate release dosage form comprising an equal amount of gabapentin, and bioavailability of gabapentin is at least 80% of that provided by the immediate release dosage form comprising an equal amount of gabapentin as measured by the area under the plasma concentration-time curve, AUC_{inf}.

B. PROPOSED ACTAVIS ANDA PRODUCTS

112. Actavis seeks approval to commercially market a generic gabapentin extended-release tablet. [1] The proposed ANDA products are [redacted] of the gabapentin allows the tablets to be taken [redacted] opposed to multiple times a day as required by immediate release gabapentin dosage forms. [redacted]

[1] [redacted] *See* ECF 328, pp. 29, 33-35 [Stip. Fact and Supp. Stip. Fact].

. This plasma curve

.

113. The proposed (Trial Tr. (Williams) 274:11–275:16; PTX000014 (ACTGAB000000330).)

.

114. .

(Trial Tr. (Williams) 290:1-10; PTX000136 (ACTGAB000321131).)

C. ACTAVIS HAS STIPULATED TO DIRECTLY INFRINGING THE ASSERTED CLAIMS OF THE '332 AND '992 PATENTS

115.

(JTX006). (ECF 328, p. 34 [Supp. Stip. Facts], ¶ 11.)

116.

(ECF 328, p. 35 [Supp. Stip. Facts], ¶ 13.)

D. ACTAVIS HAS STIPULATED THAT ITS ANDA PRODUCTS AND/OR ADMINISTRATION OF ITS ANDA PRODUCTS MEETS ALL ELEMENTS OF THE ASSERTED CLAIMS OF THE '927, '989 AND '756 PATENTS EXCEPT THE REQUIREMENT THAT THE DOSAGE FORMS SWELL TO INCREASE GASTRIC RETENTION

117.

('927 Patent (JTX003).) ECF 328, p. 33 [Supp. Stip. Facts], ¶ 5.

118. Thus, for example,

119. Independent Claim 17 of the '927 Patent reads as follows:

> A method of treating neuropathic pain in a mammal comprising administering a therapeutically effective amount of a daily dosage of about 100 mg to about 4800 mg of gabapentin or a pharmaceutically acceptable salt thereof, dispersed in a gastric retained dosage form to the mammal in which a fed mode has been induced, wherein the dosage form comprises a single polymer matrix comprising at least one swellable hydrophilic polymer that swells in a dimensionally unrestrained manner by imbibing water to increase its size to promote gastric retention of the dosage form in the stomach of the mammal, and wherein upon contact with water, gabapentin is released by

diffusion from the dosage form over a period of at least five hours and at least 40 wt% of the gabapentin is retained in the dosage form one hour after administration.

120. Asserted dependent Claim 18 of the '927 Patent reads as follows:

The method of claim 17 wherein the dosage form is administered once-daily

121. [redacted] ('989 Patent (JTX004).) ECF 328, pp. 33-34 [Supp. Stip. Facts], ¶ 7.)

122. [redacted] ('756 Patent (JTX005).) ECF 328, p. 34 [Supp. Stip. Facts], ¶ 9.)

123. [redacted]

[redacted] ('280 Patent (JTX002), 17:51-55.) ECF 328, p. 18 [Stip. Facts], ¶¶ 51-52; *Id*. p. 32 [Supp. Stip. Facts], ¶ 3.)

E. CLAIM CONSTRUCTION RELEVANT TO THE SINGLE DISPUTED "SWELLS . . . GASTRIC RETENTION" ELEMENT OF THE '927, '989 AND '756 GABAPENTIN PATENTS

124. In *Depomed v. Lupin* (No. C-09-5587 PJH) Judge Phyllis Hamilton construed the terms:

> "said polymeric matrix being one that swells upon imbibition of water thereby attaining a size large enough to promote retention in the stomach during said fed mode" ('475 Patent)
>
> "Said dosage form being one that when swollen in a dimensionally unrestricted manner as a result of imbibition of water is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during the fed mode." ('280 Patent)

(ECF 107 [Order Construing Claims, No. C-09-5587 PJH] at 7-12.) Judge Hamilton stated that "[i]t is inherent in the meaning of 'swell' that the dosage form will increase in size. All that is necessary is that the polymeric matrix that comprises the dosage form must swell to a size large enough so that the dosage form is retained in the stomach for some period of time." *Id*. at 10-11. She construed both of the terms to mean "the dosage form, which comprises a polymeric matrix, increases in size due to the ingress of water, such that when the dosage form is introduced into the stomach in the fed mode, the dosage form remains in the stomach for several hours." *Id*. at 12.

125. This language was similarly construed by Justice Breyer in *Depomed, Inc. v. Ivax Corp.* to mean "such that when introduced into the stomach in the fed mode, the dosage form remains in the stomach for several hours." (ECF 76, p. 20, No. C-06-00100 CRB (N.D. Cal. 2006).)

126. In *Depomed v. Sun Pharma Global FZE, et al.* (Case No. 3:11-CV-03553 JAP (TJB)) Judge Joel A. Pisano adopted Judge Hamilton's construction for these same two terms. (ECF 66 [Memorandum Opinion, No. 3:11-CV-3553 JAP (TJB)] at 15.)

127. In this case, Actavis requested that a portion of the claim terms in the '475 and '280 Patent again be construed along with similar terms in the '989, '927 and '756 Patents. (ECF 188 [Wettre Ltr to Court encl. Revs'd. Jt. Claim Construction and Supp. Ev.].)

- Thereby attaining a size large enough to promote retention in the stomach during said fed mode ('475 Patent (JTX008)).[2]
- Is of a size exceeding the pyloric diameter in the fed mode to promote retention in the stomach during said fed mode ('280 Patent (JTX002)).
- To increase its size to promote gastric retention of the dosage form in the stomach of the mammal ('927 Patent (JTX003)).
- To increase its size to promote gastric retention of the dosage form in the stomach in a fed mode ('989 & '756 Patent (JTX004 and JTX005)).

128. Defendants provided new claim constructions for each of the claim elements in their entirety – not just the "gastric retention" or "retention in the

[2] Depomed subsequently withdrew the '475 Patent to streamline the trial.

stomach" portions. (ECF 139 [Defendants' Joint Opening Markman Brief] at 15-16 (*e.g.*, Defendants providing the construction "is of a size exceeding the pyloric diameter in the fed mode such that when the dosage form is introduced into the stomach in the fed mode, the dosage form remains in the stomach for the duration of drug delivery" for the '280 Patent).) Depomed requested that the Court maintain its prior construction from *Depomed v. Sun* and apply it to the previously unconstrued claims elements from the '927, '989, and '756 Patents. (ECF 138 [Depomed, Inc.'s Opening Markman Submission] at 12-18, 21-22.)

129. The Court rejected the Defendants' new constructions and adopted its earlier construction – "such that when the dosage form is introduced into the stomach in the fed mode, the dosage form remains in the stomach for several hours" – to all of the above disputed gastric retention terms from the patents-in-suit. (ECF 251, pp. 6-11, [Opinion].)

F. ACTAVIS' ANDA PRODUCTS MEET THE ONLY DISPUTED CLAIM ELEMENT IN THE ASSERTED '927, '989 AND '756 PATENTS OF "SWELLS . . . . TO INCREASE ITS SIZE TO PROMOTE GASTRIC RETENTION"

1. Proof Point 1. Actavis States in Its Proposed Label That the ANDA Products Swell in Gastric Fluid and Has Stipulated That the ANDA Products Release Drug to the Upper Gastrointestinal Tract

130. The proposed Actavis ANDA labeling states [redacted]

[redacted]

[redacted] (Trial Tr. (Hopfenberg) 457:16-18; PTX000136 (ACTGAB000321121).) This means that the tablet [redacted]. (Trial Tr. (Annunziata) 163:4–17; 238:18-239:3.)

131. [redacted]. (ECF 328, pp. 32, 34 & 35 [Supp. Stip. Facts], ¶¶ 1, 11, 13. (*See* '962, '332, '992 Patent Claims (JTX001, JTX006-7), *supra*.)

2. Actavis' Proposed ANDA Products Use Hydrophilic Polymers Known to Swell in Gastric Fluid

132. The proposed Actavis ANDA labeling states [redacted] (Trial Tr. (Annunziata) 163:4-17; PTX000136 (ACTGAB000321121).) [redacted] (Trial Tr. (Williams) 271:17–22; PTX000014 (ACTGAB000000330).) [redacted] (Trial Tr. (Hopfenberg) 458:5-23; Trial Tr. (Williams) 270:10–271:8; PTX0-136 (ACTGAB000321121).)

3. Actavis' Proposed ANDA Products Use Similar Swellable Polymers And Result in Similar Drug Release Rates as Gralise® Tablets Which Embody the Asserted Gabapentin Patent Claims

133. The Actavis ANDA sets out the composition and percentages of the Actavis ANDA Products as follows:

PTX000014 (ACTGAB000000330).

134. The Actavis ANDA states that

(Trial Tr. (Williams) 273:7-19; Trial Tr. (Hejazi) 61:14-18; PTX000014 (ACTGAB000000336).)

(ECF 328, p. 21 [Stip. Facts] ¶¶ 111-116. (Trial Tr. (Williams) 272:12–273:23; PTX000014 (ACTGAB000000336); *see* Actavis Proposed ANDA Product Section, *supra.*)

Table 6 is as follows:

(PTX000014 (ACTGAB000000336).)

135. (Trial Tr. (Williams) 271:17-22; 273:1-9.)

[redacted] (Trial Tr. (Williams) 270:23 – 271:8.)

136. [redacted] (Trial Tr. (Williams) 273:10-23; PTX000014.) [redacted] (*Id.*)

137. [redacted] (Trial Tr. (Williams) 274:11 – 275:16; PTX000014 (ACTGAB000000330).) [redacted] (*Id.*) [redacted] (*Id.*)

138. To develop a generic version of the Depomed Gralise® product, Actavis considered the Depomed patents and patent applications to guess at the Gralise® formulation. (Trial Tr. (Hejazi) 52:1-20.) Based on the Depomed patents

and applications, Actavis designed an in-house reference, [redacted], which represented their best understanding of the formulation of Gralise. (Trial Tr. (Hejazi) 53:10-19; PTX000014 (ACTGAB000000336).)

139. [redacted] (Trial Tr. (Hejazi) 57:12-15; 61:22 – 62:3; PTX000014 (ACTGAB000000336).) [redacted] (Trial Tr. (Hejazi) 61:14-18; PTX000014 (ACTGAB000000336).)

140. The Actavis ANDA product uses [redacted] (Trial Tr. (Hejazi) 58:8-20; 61:8-13.) [redacted] (Trial Tr. (Hejazi) 61:4-7; PTX000014 (ACTGAB000000336).) [redacted] (Trial Tr. (Hejazi) 53:20-24; 56:19 – 57:7; PTX000039.) [redacted] (Trial Tr. (Hejazi) 72:10-19.)

141. Actavis also understood that [redacted] In a May 2011 email chain discussing [redacted] Radi Hejazi explained that [redacted] (PTX000062; Trial Tr. (Hejazi) 74:13-75:13.)

4. Proof Point 4. The Stipulated Diffusion Release of the Actavis ANDA Products *In Vivo* Requires that the Tablets Swell

142. [redacted] *See* ECF 328, p. 32, 33 & 34, [Supp. Stip. Facts], ¶¶ 3, 5, 7 and 11. ('927 and '989 Patent Claims, *supra* (JTX003-4).) Gabapentin is a highly soluble drug. (Trial Tr. (Williams) 263:10-17.) The diffusion of highly soluble drugs, like gabapentin, [redacted]. (Trial Tr. (Williams) 265:9-19.) These [redacted] serve as a [redacted]. (*Id*.) The highly water-soluble gabapentin quickly dissolves and [redacted]. (*Id*.) It is the [redacted] like gabapentin out of the dosage form. (Trial Tr. (Williams) 266:21–24.)

143. Release of the crystalline drug, gabapentin, from a controlled release dosage form [redacted] requires the ingress of water into the dosage form, which changes the nature of the dosage from to a softer, swollen form. (Trial Tr. (Hopfenberg) 453:16 – 454:14). If the Actavis ANDA Products [redacted] swelling, the release would be similar to an immediate release tablet because there would be no barrier formed by the swelling and hydrating polymers. (Trial Tr. (Williams) 279:1-7.)

144. The Actavis proposed labeling states "[redacted]." (PTX000136 (ACTGAB000321121).) [redacted] (Trial Tr. (Williams) 274:2 – 277:1.)

145. If there were grinding down or breaking of the Actavis ANDA Products *in vivo*, that would result in a much faster release of the gabapentin and change the pharmacokinetic data. (Trial Tr. (Williams) 267:3-18; 302:15 – 303:5.) [redacted] ECF 328, pp. 33-34 [Supp. Stip. Facts], ¶¶ 5, 7 and 9. (Trial Tr. (Williams) 267:3-18; '927 and '989 Patents Claims, *supra* (JTX003-004).)

146. [redacted] ECF 328, p. 32 [Supp. Stip. Facts], ¶ 3. ('280 Patent Claim (JTX002), *supra*.)

5. Proof Point 5. Actavis ANDA Products Show Unrestrained Swelling, Mass Gain Consistent With Water Uptake in *In Vitro* Studies

a. Actavis FDA Swelling Study Shows Swelling of the Actavis ANDA Products in Gastric Fluid

147. [redacted] (Trial Tr. (Hopfenberg) 459:4-18; Trial Tr. (Annunziata) 166:12–167:24; 255:1-23; PTX000135 (ACTGAB000320623).)

148. [redacted] (Trial Tr. (Hopfenberg) 460:3-461:7; Trial Tr. (Hejazi) 64:22-24, 66:24-67:7; Trial Tr.

(Williams) 277:7–24, 278:6–15; PTX000135 (ACTGAB000320624).) The 300 mg tablet increased to [redacted]. (Trial Tr. (Annunziata) 207:2–208:14.) The 600 milligram tablets increased to [redacted]. (*Id.*) The [redacted] is set forth in PTX000135 as follows:

[redacted]

PTX000135 (ACTGAB000320624)

149. [redacted] (Trial Tr. (Hopfenberg) 461:10-19; Trial Tr. (Hejazi) 62:16 – 63:25, 66:24 – 67:7; PTX000135 (ACTGAB000320624).) (Trial Tr. (Annunziata) 208:15–209:21; Trial Tr. (Williams) 277:7-24.) [redacted]

[redacted] (*Id.*) [redacted]

[redacted]

[redacted]

[redacted]

[redacted]:

[redacted]

(PTX000135 (ACTGAB000320624).)

150. [redacted] (Trial Tr. (Annunziata) 208:15 – 209:21.)

151. Actavis' supplemental ANDA submission states [redacted]

[redacted]" (Trial Tr. (Annunziata) 211:8–10; PTX000135 (ACTGAB000320626).)

b. EAG Swelling Study Shows Swelling of the Actavis ANDA Product in Gastric Fluid

152. [redacted] performed by Evans Analytical Group on the Actavis ANDA Product show that the tablets [redacted] (Trial Tr. (Hopfenberg) 462:7-463:4; PTX000238.)

153. Depomed's independent expert, Eden Tesfu, oversaw tests of [redacted] at the request of counsel. (Trial Tr. (Tesfu) 94:10-20; PTX000241.) Under Dr. Tesfu's guidance, EAG Technicians measured the [redacted] of the Actavis ANDA Products after [redacted]

154. The data provided by EAG also show that the [redacted] (Trial Tr. (Williams) 278:16–25, 279:8-19; Trial Tr. (Annunziata) 211:20 – 212:21; PTX000238 (DEPOACT0114342.1).) [redacted] (Trial Tr. (Annunziata) 212:22 – 213:9; PTX000238 (DEPOACT0114342.1).) [redacted]

[redacted] (Trial Tr. (Annunziata) 212:22–213:17.) [redacted]

[redacted]

[redacted]

(PTX000238 (DEPOACT0114342.1).

155. [redacted] studies performed by Evans Analytical Group on the Actavis 300 mg tablet show that the tablets [redacted] (Trial Tr. (Hopfenberg) 463:5-19; PTX000238

(DEPOACT0114340.1).) EAG data shows that Actavis' 300 mg tablet [redacted] The mass of the 300 mg tablet after one hour in simulated gastric fluid i[redacted] The [redacted] each make it more likely that the tablet [redacted] (Trial Tr. (Annunziata) 214:6–21.) The data from the 300 mg Actavis ANDA Product and the Gralise 300 mg tablet [redacted] is set forth in the following chart:

(PTX000238 (DEPOACT0114340.1).)

156. Pictures provided by EAG show that the 300 and 600 mg Actavis ANDA product tablets [redacted] (Trial Tr. (Annunziata) 215:1–216:18.) The 300 mg tablets [redacted]. (PTX000317.)

300 Actavis ANDA Products in Water (PTX000317 at 3 and 7.)

300 Actavis ANDA Products in mSGF (PTX000317 at 9 and 12.)

157. Longer [redacted] with the 600 mg Actavis ANDA tablet, which [redacted] (*See* F(3), *supra*), shows that it [redacted] (PTX000320 at 3, 6, 9, 12, 16; *see also* PTX000238.)

600 mg Actavis ANDA Products

1 hour post Immersion **8 hours post immersion**

DEPOACT0114309.1 DEPOACT0114333.1

10 hour post Immersion **14 hours post immersion**

DEPOACT0114315.1 DEPOACT0114321.1

6. Proof Point 6. Dr. Williams Opined That the Dosage Forms "Swell in a Dimensionally unrestrained Manner by imbibing Water to Increase Its Size," as Required by the First Part of the Disputed Element

158. Dr. Robert O. Williams – Dr. Williams was accepted by the Court as an expert in the field of formulation and pharmaceutical sciences. (Trial Tr. (Williams) 264:4-7.) Dr. Williams testified as to the ingredients and swelling properties of the Actavis proposed ANDA product and Gralise tablets. (Trial Tr. (Williams), 260-309.)

159. Dr. Williams opined that the foregoing evidence showed that the Actavis ANDA Products have "at least one swellable hydrophilic polymer that swells in a dimensionally unrestrained manner by imbibing water to increase its

size" as required by (i) asserted claims 18, 25, 26, 34, 61 and 62 of the '927 Patent, (ii) asserted claims 1, 2, 5, 6, 7 and 11 of the '756 Patent, and (iii) asserted claim 10 of the '989 Patent. (Trial Tr. (Williams) 268:10 – 269:14.) He based his opinion on the foregoing findings of fact 130-158, *supra*.

7. Proof Point 7. The Actavis ANDA Products' Swelling Promotes Gastric Retention in the Stomach

160. Upon the intake of food, the stomach enters the fed mode in which the stomach takes big chunks of food and makes them into small chunks of food. (Trial Tr. (Annunziata) 151:13-15.) In fed mode, the pH of the stomach changes and the stomach begins to contract. (Trial Tr. (Annunziata) 152:14-18.) Gentle waves of contractions start at the top, at the fundus, and proceed through the stomach to the antrum while the pylorus is clenched. (*Id*.) The pylorus holds large particles in the stomach so that they can be further digested and allows smaller particles, about 2-4 mm, through to the small bowel. (Trial Tr. (Annunziata) 154:8-13, 217:16 – 218:4.) The pylorus is closed during the terminal antrum contraction and is open for brief periods of time during the retropelling wave in which it opens like a relief valve to approximately 12.8 millimeters. (Trial Tr. (Annunziata) 144:25 – 145:11, 155:10-18; 159:9-13, 233:18 – 234:1.) The retropelling wave pushes the remaining particles back up into the body of the stomach to then repeat the process. (Trial Tr. (Annunziata) 152:9 – 153:1, 153:13-15.) Fed mode may last between 45

minutes and six hours depending upon the meal ingested. The average time is approximately four hours. (Trial Tr. (Annunziata) 230:4-21.)

161. "Meals of larger weight and kcal content are associated with longer emptying time, for both solids and liquids." (Trial Tr. (Annunziata) 257:12-15; PTX000469 (DEPOACT0981018).) The density, weight, or shape of a particle may make it more difficult to exit the stomach. (Trial Tr. (Annunziata) 156:15–18.) A larger or swollen particle is less likely it is to leave the stomach. (Trial Tr. (Annunziata) 155:19-22, 156:4-11, 158:16-20, 209:5-21.) Once a particle gets towards a centimeter in size it is very unlikely to leave the stomach. (Trial Tr. (Annunziata) 156:4-11.) An elongated shape is likely to be repulsed from the pylorus when it clenches and is retropelled back into the stomach. (Trial Tr. (Annunziata) 156:15-23, 158:14-15.) The increase in mass also makes it more likely to be retained. (Trial Tr. (Annunziata) 218:20-22.)

162. As the Actavis ANDA product tablet elongates and approaches the pyloric channel it will tend to be retropelled when the pyloric channel clenches. The retropelling wave will take the tablet back to the top of the stomach. (Trial Tr. (Annunziata) 218:5-13.) A long tablet is likely to be retained even when the pylorus is open as it may approach the pylorus sideways. (Trial Tr. (Annunziata) 219:1-10.) The increase in size of the short axis also makes it less likely that the tablet will pass through the pylorus. (Trial Tr. (Annunziata) 219:11-16.) Although

the tablets swell and become softer the swollen size is still sufficient to prevent passage through the pylorus. (Trial Tr. (Annunziata) 224:16-20.)

163. Actavis' expert, Dr. David Friend, agreed that as a dosage form swells in size, its size will probably enhance gastric retention in the fed mode and that a larger particle would be less likely to empty from the fed stomach than a smaller one. (Trial Tr. (Friend) 536:24 – 537:5, 540:1-9.)

164. Dr. Friend considers the human pylorus to have an average size of 12-13 mm, but he did not consider that the pylorus clenches during the fed state despite being aware of that phenomenon. (Trial Tr. (Friend) 540:16-18, 540:10-15.)

8. Proof Point 8. Actavis ANDA Products Remain in the Stomach for Several Hours as Evidenced by the Label and the Pharmacokinetic Data

a. Actavis' Proposed Label Indicates That the Actavis ANDA Products Are Gastrically Retained

165. Actavis' proposed labeling states [redacted] (PTX000136 (DEPOACT0321105).) A POSITA understands that when someone [redacted], they typically intend for it to be retained in the stomach. (Trial Tr. (Annunziata) 220:1-11.) [redacted] indicates to the POSITA that Actavis [redacted]

[redacted], otherwise it could be [redacted]. (Trial Tr. (Annunziata) 163:22 – 164:11.)

166. Actavis' proposed labeling states [redacted] (PTX000136 (ACTGAB000321122).) This informs the POSITA that the [redacted] (Trial Tr. (Annunziata) 165:10-21.)

167. Actavis' proposed labeling states [redacted] (PTX000136 (DEPOACT0321123).) A POSITA understands this to mean that [redacted] Trial Tr. (Annunziata) 164:12 – 165:1.) The [redacted] indicates that Actavis wants the tablet to [redacted] because the tablet has [redacted] (Trial Tr. (Annunziata) 217:6-15.)

b. Actavis Fed/Fasted Pharmacokinetic Data and Bioequivalence Waiver Shows Gastric Retention of the Dosage Form Over Several Hours

168. Dr. Hartmut Derendorf was accepted as an expert in the field of pharmacokinetics by the Court. (Trial Tr. (Derendorf), 336:5-8.) Dr. Derendorf testified on the pharmacokinetic data from the Actavis ANDA and evidence for gastric retention. (Trial Tr. (Derendorf), 332-367.)

169. Actavis provided no expert witness to oppose Dr. Derendorf's testimony that the pharmacokinetic data shows that the Actavis ANDA products are gastric retained or to deny in any way that the Actavis ANDA products are gastric retained. (Trial Tr. (Friend) 541:2-24.)

170. Performing fed and fasting pharmacokinetic studies measuring the Cmax, Tmax and AUC_{0-t} are a standard requirement with the FDA. (Trial Tr. (Venugopal) 312:25 – 313:9.) Cmax is the maximum concentration the drug reaches in blood plasma after administration. (Trial Tr. (Venugopal) 315:20-22, 316:8-10.) Tmax is a measure of the time to maximum concentration of the drug (Cmax) in the subject's blood plasma. (Trial Tr. (Venugopal) 315:20-24, 316:11-14.) AUC is the "area under the curve" measured from time zero to the last blood draw point of the study and references the exposure of the drug in the subject. (Trial Tr. (Venugopal) 316:3-7, 315:25 – 316:2.)

171. Pre-clinical studies in dogs by Stevenson show that gabapentin absorption takes place in the small intestines but largely does not occur in the large intestines. (Trial Tr. (Derendorf) 339:11-16; PTX000500 (Gralise_JDG_00000602).) Stevenson states "[c]omparison of the blood-level data from oral and jejunal administration of gabapentin indicates that there is substantial absorption from the duodenum and upper jejunum. Most important, gabapentin plasma levels from colonic administration are substantially lower than those obtained from oral and upper intestinal administration." (Trial Tr. (Derendorf) 339:17 – 340:2; PTX000500 (Gralise_JDG_00000602).)

172. Gabapentin transporters, proteins that take up the drug and move it to the other side of the intestinal membrane, are only located in a small range of the small intestine requiring that the drug be at the right place at the right time to be taken up. (Trial Tr. (Derendorf) 338:5-13, 337:2 – 338:3.) If the dosage form passes by the window of absorption too rapidly before the drug is released, the dosage form will not work well because gabapentin will be released into the large intestine where it is not absorbed. (Trial Tr. (Derendorf) 340:20-24.)

173. Gabapentin transporters are present in limited numbers. Therefore, too much drug saturates them, preventing further drug uptake. (Trial Tr. (Derendorf) 339:3-8.) Upon transporter saturation, the uptake of gabapentin will no longer go up proportionately with an increase of gabapentin dose. Although the amount of

gabapentin provided may go up, the percent absorption will go down. (Trial Tr. (Derendorf) 341:14-24.) The exposure of the transporters to drug has to be just right for the system to be efficient.

174. The stomach's gastric emptying time, but not the small intestinal transit time, is affected by food. (Trial Tr. (Derendorf) 344:3-13.) It takes approximately three hours for a dosage form to pass through the small intestines. (Trial Tr. (Derendorf) 340:15-19.)

175. In a study by Dr. Davis from the University of Nottingham in which he summarizes 201 studies, he concludes that the small intestinal transit time is about three hours plus or minus one hour and that intestinal transit time is independent of the fed state (Trial Tr. (Derendorf) 343:12 – 344:10; PTX000525 (DEPOACT0981978-981980).) This is in agreement with a 2002 chapter by Actavis's expert Dr. Mayersohn on pharmaceutics, in which he wrote "[o]nce emptied from the stomach, materials (such as pellets and tablets) will move along the small intestine and reach the ileocecal valve in about three hours." (Trial Tr. (Derendorf) 345:10-24; PTX000521 (DEPOACT0982017).) Dr. Mayersohn also wrote "[f]urthermore, food appears not to influence intestinal transit as it does gastric emptying." (Trial Tr. (Derendorf) 345:15 – 346:8; PTX000521 (DEPOACT0982017).)

176. In the case of gastric retention, the dosage form remains in the stomach and releases the drug from that location. The drug moves down from the stomach over a long period of time to the small intestine and can be absorbed by transporters there. (Trial Tr. (Derendorf) 338:23 – 339:2.) Without gastric retention, the dosage form will leave the stomach earlier and move into the small and large intestines. Without gastric retention, there would be a much earlier Tmax and incomplete absorption because the drug would be released when it is no longer able to be absorbed in the upper small intestines. (Trial Tr. (Derendorf) 349:2-14.) Gastric retention is essential for sustained exposure of gabapentin to its site of absorption in the upper small intestines, and the only way to achieve that is by anchoring the dosage form in the stomach allowing the drug to come out of the dosage form slowly over time. (Trial Tr. (Derendorf) 344:18 – 345:6.)

177. Actavis had [redacted] performed by [redacted]. (Trial Tr. (Venugopal) 315:2-8, 327:7 – 328:9.)

(PTX000019 (ACTGAB000000555).)

178. Under the 600 mg Actavis ANDA Product achieved an and the Gralise 600 mg product achieved a . (Trial Tr. (Venugopal) 316:16 – 317:7; PTX000019 (ACTGAB000000555).) In the the Actavis ANDA Product had a and Gralise 600 mg had a . (Trial Tr. (Venugopal) 317:21 – 318:1; PTX000019 (ACTGAB000000555).) The 600 mg Actavis ANDA Product had an and the Gralise 600 mg tablet had an . (Trial Tr. (Venugopal) 318:9-18; PTX000019 (ACTGAB000000555).)

179. Actavis had a

performed by . (Trial Tr. (Venugopal) 319:13 – 320:1.)

(PTX000020 (ACTGAB000000581).)

180. Under the 600 mg Actavis ANDA Product achieved a and Gralise 600 mg tablets achieved a (Trial Tr. (Venugopal) 320:2-15; PTX000020 (ACTGAB000000581).) Under the of the 600 mg Actavis ANDA Product is and the of the Gralise 600 mg tablets is . (Trial Tr. (Venugopal) 320:19-321:1; PTX000020 (ACTGAB000000581).) Under the average

for the 600 mg Actavis ANDA product and [redacted] for the Gralise 600 mg tablets (PTX0000020 (ACTGAB000000581).)

181. Subjects given the 600 mg Actavis ANDA Product achieve a [redacted] which [redacted]. (Trial Tr. (Venugopal) 321:8-15.) The [redacted] of subjects given the 600 mg Actavis ANDA Product was [redacted] and [redacted]. (Trial Tr. (Venugopal) 321:16-22.)

182. A comparison of the 600 mg Actavis ANDA Product [redacted] shows that the [redacted] when the dosage form is given in [redacted]. (Trial Tr. (Derendorf) 349:18 – 350:16, 346:25 – 348:21.) PTX000506 [redacted] (Trial T. (Venugopal) 328:1-9.)

[redacted]

(PTX000506 (ACTGAB000005207).)

183. This curve is consistent with the [redacted] (Trial Tr. (Derendorf) 348:22 – 349:14.) [redacted] (Trial Tr. (Derendorf) 349:18 – 350:16; PTX000506 (ACTGAB000005207).) PTX000034 shows the results of a bioequivalence study performed [redacted] or in "[redacted] (Trial Tr. (Venugopal) 327:11-22.)

[redacted]

(PTX0000034 (ACTGAB000008356).)

184. The 600 mg Actavis ANDA Product data in [redacted] shows [redacted] (Trial Tr. (Derendorf) 348:1-21; PTX0000034 (ACTGAB000008356).)

185. Actavis [redacted]

. (Trial Tr. (Venugopal) 326:17–25; PTX000023 (ACTGAB000000659).) Subjects given the 300 mg Actavis ANDA Product (Trial Tr. (Venugopal) 323:1–324:1; PTX000023 (ACTGAB000000659).) Subjects given the Gralise 300 mg tablets (Trial Tr. (Venugopal) 324:3–9; PTX000023 (ACTGAB000000659).) The Actavis 300 mg dosage form has . (Trial Tr. (Derendorf) 355:10–24; PTX000023 (ACTGAB000000659).)

186. Actavis submitted a waiver for 300 mg indicating that the it was not necessary because the once daily 300 and 600 mg tablets are proportionally similar (*i.e.* the two products are equivalent). (Trial Tr. (Derendorf) 356:3–18.) In its request for waiver, Actavis also points out that the 300 and 600 mg Actavis ANDA Products have (Trial Tr. (Derendorf) 356:21–357:13.)

187. Actavis based on the . (Trial Tr. (Venugopal) 317:4-318:19). Section 2.3 of the Actavis ANDA concludes

[redacted] (PTX000014 (ACTGAB000000370).)

c. Deconvolution Data of Fed Subjects Administered the 600 mg Actavis ANDA Product Shows Gastric Retention

188. The pharmacokinetics of a drug can be affected by its level of absorption, distribution in the body to various tissues, metabolism, and the elimination rate. (Trial Tr. (Derendorf) 337:15-21).

189. The Tmax value, which is the time at which the plasma concentration peaks, indicates that up to that time point there is still drug input to the site of absorption because plasma levels would not continue to go up if there were no drug coming to the site of absorption. (Trial Tr. (Derendorf) 348:1-14). [redacted] for the 600 mg Actavis ANDA product [redacted] (*Id.*)

190. The cumulative amount of drug that enters the body over time can be shown by stripping away the elimination of the gabapentin from the 600 mg Actavis ANDA Product's pharmacokinetic results from its [redacted] using deconvolution. (Trial Tr. (Derendorf) 351:17 – 352:18; PTX000020.) This allows for the calculation of the absorption profile of the gabapentin tablets. This shows that for both Actavis ANDA Products and Gralise tablets [redacted]. (*Id.*) The only way that the site of absorption could be

exposed to gabapentin for that length of time is [redacted] of the Actavis ANDA Products [redacted]. (Trial Tr. (Derendorf) 354:9-15).

9. Proof Point 9. Actavis ANDA Products' Data Similarity to the Gralise Tablets That Actavis Has Stipulated Are Gastrically-Retained Shows That the Actavis ANDA Products Are Also Gastrically-Retained

191. [redacted]

ECF 328, p. 33 [Supp. Stip. Facts] ¶ 5. (Trial Tr. (Annunziata) 160:21–161:9; '927 Patent Claims (JTX003), *supra*.) [redacted].

192. [redacted] *See* ECF 328, p. 29 [Stip. Facts], ¶¶ 111-116.

193. [redacted]

(JTX003 and JTX005. *See* ECF 328, pp. 33-34 [Supp. Stip. Facts], ¶¶ 5 and 9.)

194. Actavis [redacted] under various conditions comparing the Actavis ANDA Product to its Gralise® dosage form counterpart. (Trial Tr. (Derendorf) 357:3-359:20). These are analyzed using a

metric for similarity called an "F2" in which any F2 measurement over 50 is accepted by the FDA as being similar – i.e. having equivalent rate of drug release *in vitro*. (Trial Tr. (Derendorf) 357:4-13).

195. The Actavis ANDA's Report [redacted] shows that [redacted]

- [redacted]
  - [redacted] (PTX000012 (ACTGAB000000234)).
  - [redacted] (PTX000012 (ACTGAB000000244)).
  - [redacted] (PTX000012 (ACTGAB000000254)).
  - [redacted] (PTX000012 (ACTGAB000000264)).
  - [redacted] (PTX000012 (ACTGAB000000274)).
- [redacted]
  - [redacted] (PTX000012 (ACTGAB000000235)).
  - [redacted] (PTX000012 (ACTGAB000000245)).
  - [redacted] (PTX000012 (ACTGAB000000255)).

- [redacted] (PTX000012 (ACTGAB000000265)).
- [redacted] (PTX000012 (ACTGAB000000275)).

196. Actavis ANDA Products [redacted] which Actavis [redacted] This indicates that these tablets have the same mechanisms (*e.g.*, gastric retention, absorption rates) otherwise there would be differences in [redacted]. (Trial Tr. (Derendorf) 357:17–359:2.) (*See* Actavis Fed/Fasted Pharmacokinetic Data, *supra,* FOF 177-187.)

10. Dr. Derendorf and Dr. Annunziata Opined That the Actavis ANDA Products Were Gastrically-Retained Within the Meaning of the Asserted Claims of the '927, '989 and '756 Patents While Dr. Friend Failed to Opine They Were Not

197. Dr. Derendorf based on the foregoing facts opined that the Actavis ANDA Products meet the claim element of increase its size to promote gastric retention of the dosage form within the meaning of the asserted claims of the '756, '927 and '989 Patents. (Trial Tr. (Derendorf) 336:20 – 337:6, 359:3-19.)

198. Dr. Annunziata opined that [redacted] (Trial Tr. (Annunziata) 162:1-10; 217:1-5; 219:17 – 221:18.)

199. Actavis' expert, Dr. David Friend agreed that the *in vitro* swelling data shows that the Gralise tablets and the Actavis ANDA Products swell in a similar manner and to a similar extent. (Trial Tr. (Friend) 535:16 – 536:19.)

200. When rendering his opinions on *in vivo* swelling in this case, Dr. Friend did not consider that Actavis [redacted] (Trial Tr. (Friend) 537:6 – 538:1.) Claim 17 of the '927 Patent requires that the tablet, when given to a mammal, swells to promote gastric retention. (Trial Tr. (Friend) 537:20 – 538:19; *see* '927 Patent claims, *supra*.) Actavis [redacted]. ECF 328, p. 33 [Supp. Stip. Facts], ¶5.

201. Dr. Friend never testified that the Actavis ANDA Products would not be gastrically-retained within the meaning of the asserted gabapentin patent claims.

G. SUMMARY OF EVIDENCE THAT ACTAVIS ANDA PRODUCTS LITERALLY INFRINGE THE ASSERTED CLAIMS OF THE '927, '989 AND '756 PATENTS

202. Based on at least the following facts, Depomed has shown by a preponderance of the evidence that the Actavis ANDA Products literally infringe the disputed element of "swells . . . to promote gastric retention," and as such, all elements of the asserted claims for direct and literal infringement are met:

a. The [redacted] referenced drug Gralise as an embodiment of the asserted '927, '989 and '756 Patent claims;

b. [redacted];

c. [redacted]

d. The characteristics of the stomach and physiology in the fed mode;

e. [redacted] and that gabapentin is absorbed primarily in the upper small intestines by saturable transporters and is consistent with an intact dosage form residing in the stomach for several hours and slowly releasing drug by diffusion;

[redacted]

g. The *in vitro* release profile data of the Actavis ANDA Products and the reference Gralise products;

h. The expert testimony of Dr. Annunziata, Dr. Williams and Dr. Derendorf;

i. The non-credible expert testimony of Dr. Friend who did not opine that the Actavis ANDA Products were *not* gastrically-retained within the meaning of the asserted claims.

H. ACTAVIS WILL CONTRIBUTE UNDER 35 U.S.C. § 271(C) TO THE INFRINGEMENT OF THE ASSERTED METHOD CLAIMS OF THE '927, '756, '332 AND '992 PATENTS

1. Patients and Physicians Will Directly Infringe the Asserted Method Claims in the '927, '756, '332 and '992 Patents by Administering the Actavis ANDA Products To Treat a Condition, Including Neuropathic Pain

203. The proposed Actavis ANDA label instructs that "[redacted]

[redacted]

[redacted] which is otherwise known as postherpetic pain which is classified as a type of [redacted]. (PTX000136 (ACTGAB000321131); Trial Tr. (Williams) 290:1-10.)

204. The dosage form will be administered by a health-care professional following the label's method of treating, [redacted] (Trial Tr. (Williams) 285:5-8, 305:6-11; see DTX00031). Drug manufacturers are required to correct material misstatements in labels. (Trial Tr. (Williams) 308:4-309:2).

205. For the reasons stated above, these acts will directly infringe the asserted gabapentin patent claims.

2. Actavis Knew About the Asserted Gabapentin Patents

206. Actavis' act of writing and submitting its paragraph IV certification to the FDA and to Depomed demonstrate that it was aware of the '927, '756, '332 and '992 Patents. (Trial Tr. (Williams) 282:17 – 283:8.) *See* ECF 328, pp. 13-14 [Stip. Facts], ¶¶ 15, 16, and 18-22.)

3. Actavis' ANDA Products Are a Material Part of the Claimed Methods

207. The Actavis 300 and 600 mg dosage forms are a material part of the '927, '756, '332 and '992 Patent method claims because the methods require the administration of gabapentin in a therapeutically effective amount, for the purposes

of treating neuropathic pain or postherpetic neuralgia, or diseases responsive to a therapeutic dose of gabapentin. (Trial Tr. (Williams) 283:9–284:13; 285:3–8; 285:18–286:14; 287:15–20). [redacted]. (*See* ECF 328, pp. 33-35 [Supp. Stip. Facts], ¶¶ 5, 9, 11, 13).

208. The asserted method claims of the Patents-in-suit generally require gastric retained dosage forms with single polymer matrices made up of at least one swellable hydrophilic polymer that swells in size and dimensions in an unrestrained manner and release drug by diffusion over at least five hours. (Trial Tr. (Williams) 284:4-13). [redacted] (*See* ECF 328, pp. 33-35 [Stip. Facts], ¶¶ 5, 9, 11, 13.)

209. Therefore, the Actavis ANDA Products factually constitute a material part of the method claims, which are directed to administering the dosage form to treat a subject for a condition.

4. Actavis' ANDA Products Will Not Be Sold for Non-Infringing Uses

a. The Actavis ANDA Products Will Be Sold in Accordance With the Label to Treat Post Herpetic Neuralgia Which is a Therapeutic Use

210. The Actavis ANDA Products could not be promoted for something other than the methods described in the asserted claims because drug producers are not allowed to promote their product for anything other than what is approved in

the label. (Trial Tr. (Williams) 288:10–20). The label provided by Actavis indicates [redacted] (Trial Tr. (Williams) 289:2-10; 289:23 – 290:10; PTX000136 (ACTGAB000321105).)

b. The Actavis ANDA Products Are Indicated for Treating Postherpetic Neuralgia, a Type of Neuropathic Pain and the Data Shows That Gralise Is Sold Only To Treat Forms of Neuropathic Pain as Recited by Claims 18, 25, 26 and 61 of the '927 Patent

211. The Actavis products may not be promoted for uses other than the methods described in the asserted claims because drug producers are not allowed to promote their product for anything other than what is approved in the label. (Trial Tr. (Williams) 288:10–20). The label provided by Actavis indicates [redacted] (Trial Tr. (Williams) 289:2-10; 289:23 – 290:10.)

212. Gabapentin is approved for the treatment of postherpetic neuralgia but physicians prescribe gabapentin for other forms of neuropathic pain, but not for pain outside of the neuropathic pain. (Trial Tr. (Brown) 883:20-884:9; 884:23-885:7). Research data on the indications for which practitioners prescribe Gralise show that it is prescribed exclusively for neuropathic pain. (Trial Tr. (Brown) 886:5-24; PTX000458).

I. ACTAVIS WILL INDUCE INFRINGEMENT UNDER 35 U.S.C. § 271(B) OF THE ASSERTED METHOD CLAIMS OF THE '927, '756, '332 AND '992 PATENTS

1. The Administration of the Actavis ANDA Products Will Directly Infringe

213. As set forth in FOF 64-212, *supra*, all elements of direct infringement for the asserted method claims of the '927, '756, '332 and '992 Patents will be directly infringed upon the ANDA Products' commercialization.

2. Actavis Is Aware of the Asserted Patents

214. Actavis' writing and submission of its paragraph IV certification to the FDA and to Depomed demonstrate that it was aware of the '927, '756, '332 and '992 Patents. (Trial Tr. (Williams) 282:17–283:8.) *See* ECF 328, pp. 13-14 [Stip. Facts], ¶¶ 15, 16, and 18-22.

3. Actavis Will Knowingly Induce Infringement of Depomed's the '927, '756, '332 and '992 Patents

215. [redacted]. *See* ECF 328, pp. 33-35 [Supp. Stip. Facts], ¶¶ 5, 9, 11, 13.

216. [redacted] (Trial Tr. (Williams) 272:12–273:23; PTX000014 (ACTGAB000000336).) ECF 328, p. 29 [Stip. Facts], ¶¶ 111-116.)

217. The dosage form will be administered by a health-care professional or user following the label's method of treating, [redacted]. (Trial Tr. (Williams) 285:5-8, 305:6-11; *see* DTX00031.) [redacted] (PTX000136 (ACTGAB000321105).) Drug manufacturers are required to correct material misstatements in labels. (Trial Tr. (Williams) 308:4 – 309:2.)

218. Gabapentin is approved for the treatment of postherpetic neuralgia. (Trial Tr. (Brown) 883:20-884:9). The label provided by Actavis indicates [redacted] (Trial Tr. (Williams) 289:2–10; 289:23 – 290:10; PTX000136 (ACTGAB000321105).)

4. Actavis Specifically Intends To Induce Infringement of Depomed's Patented Method

219. [redacted]. *See* ECF 328, pp. 33-35 [Supp. Stip. Facts], ¶¶ 5, 9, 11, 13).

220. [redacted] (Trial Tr. (Williams) 272:12–273:23; PTX000014 (ACTGAB000000336).) ECF 328, p. 29 [Stip. Facts], ¶¶ 111-116. (*See also* Actavis Proposed ANDA Product Section, *supra.*)

221. The Actavis ANDA Products could not be promoted for something other than the methods described in the asserted claims because drug producers are not allowed to promote their product for anything other than what is approved in the label. (Trial Tr. (Williams) 288:10–20.) *See also* Conclusions of Law, *infra*.

222. The dosage form will be administered by a health-care professional or user following the label's method of treating, [redacted] (Trial Tr. (Williams) 285:5-8; 305:6-11; *see* DTX00031.) The proposed Actavis ANDA label instructs that [redacted] (Trial Tr. (Williams) 290:1-10.) [redacted] (PTX000136 (ACTGAB321105).) Drug manufacturers are required to correct material misstatements in labels. (Trial Tr. (Williams) 308:4 – 309:2.)\

V. PROPOSED CONCLUSIONS OF LAW – INFRINGEMENT OF THE ASSERTED GABAPENTIN PATENTS

A. BURDEN OF PROOF

223. Infringement must be proved by the patentee by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Labs. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988).

224. To meet its preponderance of the evidence burden, the patentee must show that it is more likely than not that the proposed ANDA product would, if commercially marketed, meet the claim limitations of the patent-in-suit. *See Adams Respiratory Therapeutics, Inc. v. Perrigo Co.*, 616 F.3d 1283, 1287 (Fed. Cir. 2010); *Warner-Lambert Co. v. Teva Pharms. USA, Inc.*, 418 F.3d 1326, 1341 n.15 (Fed. Cir. 2005).

225. Although the ANDA filing controls the infringement inquiry, the Court must consider "all the relevant evidence, including … other materials submitted by the accused infringer to the FDA, and other evidence provided by the parties." *Abbott Labs. v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002). The Court can also take into account any data generated from testing conducted on samples of the proposed ANDA product. *See id.* at 1375.

B. CLAIM CONSTRUCTION

226. "It is a 'bedrock principle' of patent law that 'the claims of a patent define the invention to which the patentee is entitled the right to exclude.'" *Phillips*

v. AWH Corp., 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1115 (Fed. Cir. 2004)).

227. Plain and ordinary meaning controls the construction analysis. *See N. Telecom Ltd. v. Samsung Elecs. Co., Ltd.*, 215 F.3d 1281, 1295 (Fed. Cir. 2000) ("The plain and ordinary meaning of claim language controls, unless that meaning renders the claim unclear or is overcome by a special definition that appears in the intrinsic record with reasonable clarity and precision.").

228. The Federal Circuit has repeatedly held that, in interpreting claims, it is improper to read unstated limitations into claim language. *See id.* at 1290 (phrase "aluminum and aluminum oxide" was not limited to aluminum arranged in a layer, even though the embodiments in the specification contained aluminum layers, in part because the term "layer" was not in the claim and the specification referred to aluminum both in terms of its elemental variety and as a "layer").

229. "The descriptive part of the specification aids in ascertaining the scope and meaning of the claims inasmuch as the words of the claims must be based upon the description. The specification is, thus, the primary basis for construing the claims." *Specialty Composites v. Cabot Corp.*, 845 F.2d 981, 987 (Fed. Cir. 1988) (citation omitted). In particular, "[w]here a specification does not ***require*** a limitation, that limitation should not be read from the specification into the claims."

Id. (emphasis in original) (term "plasticizer" in the claims was not limited to external plasticizers, although the examples in the specification described only externally plasticized polyvinylchloride, as the specification merely referred to plasticizers generally and even disclosed some internally plasticized polymers).

230. "It is established that 'as a general rule claims of a patent are not limited to the preferred embodiment or to the examples listed within the patent specification.'" *Glaxo Wellcome, Inc. v. Andrx Pharms., Inc.*, 344 F.3d 1226, 1233 (Fed. Cir. 2003) (quoting *Dow Chem. Co. v. U.S.*, 226 F.3d 1334, 1342 (Fed. Cir. 2000)).

231. The meaning of a claim term, therefore, is not restricted to the specific examples or embodiments set forth in the specification. *See Eolas Techs. Inc. v. Microsoft Corp.*, 399 F.3d 1325, 1336 (Fed. Cir. 2005) (phrase "executable application" included applications or components that were not standalone, even though all the disclosed embodiments in the specification described standalone programs); *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 904, 908 (Fed. Cir. 2004) (pressure jacket was not an essential component of the invention, despite the fact that all the embodiments described in the specification included a pressure jacket); *Glaxo Wellcome*, 344 F.3d at 1233 (HPMC used in the claimed mixture with bupropion hydrochloride was not limited to the particular grade and molecular weight of HPMC described in the examples in the specification); *Teleflex, Inc. v.*

Ficosa N. Am. Corp., 299 F.3d 1313, 1327-28 (Fed. Cir. 2002) (refusing to limit the term "clip" to having a "single pair of legs," even though the specification described only a single embodiment, in part because the number of embodiments was not determinative of the meaning of the claim term).

C. LEGAL STANDARD

232. It is an act of infringement to submit an application under § 505(j) of the Federal Food, Drug, and Cosmetic Act (*i.e.*, 21 U.S.C. § 355(j)) for a drug claimed in a patent or the use of which is claimed in a patent, if the purpose of such submission is to obtain approval to engage in the commercial manufacture, use, or sale of that same drug before the expiration of such patent. *See* 35 U.S.C. § 271(e)(2)(A); *see also Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1346 (Fed. Cir. 2000) ("[M]ere act of filing an ANDA constitutes infringement.").

233. The controlling question under 35 U.S.C. § 271(e)(2)(A) is whether the drug that is the subject of the ANDA will infringe the patent when approved and marketed. *See Bristol-Myers Squibb Co. v. Royce Labs., Inc.*, 69 F.3d 1130, 1135 (Fed. Cir. 1995).

234. Moreover, a party may seek a declaration under the Declaratory Judgment Act, 28 U.S.C. § 2201, that an entity will infringe in the future. The act of filing an ANDA accompanied by data sufficient to make FDA approval

imminent gives rise to a right of the patent holder for an action for infringement under the Declaratory Judgment Act. *Glaxo v. Novopharm*, 110 F.3d 1562, 1570 (Fed. Cir. 1996.)

235. A determination of infringement is a two-step analysis. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). First, the Court must construe the meaning and scope of the asserted claims of the patent-in-suit as a matter of law. *See Markman*, 52 F.3d at 976; *SmithKline*, 859 F.2d at 889. Second, the trier of fact must compare the properly-construed claims to the accused product or method to determine whether the accused product or method is within the scope of the claims. *See id.*

236. To prove infringement, the patentee must show that an accused product or method is within the claim limitations of the patent-in-suit either literally or under the doctrine of equivalents. *See Amgen Inc. v. F. Hoffmann-LaRoche Ltd.*, 580 F.3d 1340, 1374 (fed. Cir. 2009; *Warner Jenkinson Co., Inc. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 21 (1997).

237. "A patent is infringed if any claim is infringed … for each claim is a separate statement of the patented invention." *Pall Corp. v. Micron Separations*, 66 F.3d 1211, 1220 (Fed. Cir. 1995)(citations omitted).

1. Literal Infringement

238. Literal infringement exists if any one of a patent's asserted claims covers the alleged infringer's product or process. *See Markman v. Westview*, 517 U.S. 370, 374 (1996).

239. Literal infringement is shown where each limitation of at least one asserted claim of the patent-in-suit is found in the alleged infringer's product or process. *See Hormone Research Found., Inc. v. Genentech, Inc.*, 904 F.2d 1558, 1562 (Fed. Cir. 1990); *Panduit Corp. v. Dennison Mfg. Co., Inc.*, 836 F.2d 1329, 1330 n.1 (Fed. Cir. 1987).

240. Proof of literal infringement may be based on direct or indirect evidence. *See Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1372 (Fed. Cir. 2009) ("A patentee may prove infringement by any method of analysis that is probative of the fact of infringement … and circumstantial evidence may be sufficient ….") (citations omitted).

2. Direct Infringement

241. To prove direct infringement, a patentee must establish that one or more patent claims read on the accused product or method, either literally or under the doctrine of equivalents. *See Spansion, Inc. v. I.T.C.*, 629 F.3d 1331, 1349 (Fed. Cir. 2010).

242. "[I]ntent is not an element of direct infringement, whether literal or by equivalents .... Infringement is, and should remain, a strict liability offense." *Hilton Davis Chem. Co. v. Warner-Jenkinson Co. Inc.*, 62 F.3d 1512,1527 (Fed. Cir. 1995).

3. Induced Infringement

243. A party that "actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b).

244. Induced infringement under § 271(b) occurs where: (1) another party directly infringes a patent claim; (2) the inducing party intentionally encourages the acts that constitute such direct infringement; and (3) the inducing party knows that its actions will cause direct infringement. *See Global-Tech Appliances, Inc. v. SEB S.A.*, 131 S. Ct. 2060, 2068 (2011); *Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1312 (Fed. Cir. 2005).

245. To prove indirect infringement by the manufacturer of an allegedly infringing product, a patentee must show that the manufacturer's customers directly infringe the patent. *See Glenayre Elecs., Inc. v. Jackson*, 443 F.3d 851, 858 (Fed. Cir. 2006).

246. Induced infringement under 35 U.S.C. § 271(b) requires knowledge that the induced acts constitute patent infringement. *See Global-Tech*, 131 S. Ct. at 2068.

247. Willful blindness, which constitutes knowledge, requires that: (1) the defendant subjectively believes that there is a high probability that its proposed product or process infringes; and (2) the defendant take deliberate actions to avoid knowing that fact. *See id.* at 2070.

248. The trier of fact considers the totality of the circumstances in an inducement analysis. *See Abraxis Bioscience, Inc., v. Navinta, LLC*, 640 F. Supp. 2d 553, 570 (D.N.J. 2009) (Pisano, J.), *rev'd on other grounds*, 625 F.3d 1359 (Fed. Cir. 2010).

a. An Intended Product Label That Promotes Infringing Use Satisfies the Showing of an Affirmative Intent that the Product be Used to Infringe

249. Statements or actions promoting direct infringement, including "advertising an infringing use or instructing how to engage in an infringing use, show an affirmative intent that the product be used to infringe." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1059 (Fed. Cir. 2010) (inclusion of instructions in proposed label for generic budesonide inhalation suspension showed an intent to cause users to infringe the asserted method claims of treating bronchial asthma). In particular, statements made in a proposed package insert that teach users, such as physicians and patients, to use the ANDA product are sufficient to establish intent to encourage infringement of an asserted method claim. *See id.* at 1060.

250. The Federal Circuit has "long held that the sale of a product specifically labeled for use in a patented method constitutes inducement to infringe that patent …." *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 2011 WL 3235718, at *9 (Fed. Cir. July 29, 2011) (generic atomoxetine product labeled solely for the patented use to treat ADHD constituted induced infringement); *see also AstraZeneca*, 633 F.3d at 1060 ("The pertinent question is whether the proposed label instructs users to perform the patented method.").

251. Product labeling providing infringing instruction of use displays an "affirmative intent" to induce infringement that overcomes claims of non-infringing off-label uses. *AstraZeneca LP v. Apotex, Inc.*, 623 F. Supp. 2d 579, 604-605 (D.N.J 2009), *aff'd*, 633 F.3d 1042, 1060 (Fed. Cir. 2010).

252. The FDA's requirement that an ANDA filer must follow the brand name's label does not undermine the label as proof of an "affirmative intent" to induce because the ANDA filer is free to submit a Paragraph III certification, an NDA, propose label amendments to the FDA, and/or appeal to the FDA. *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1059, 1061 (Fed. Cir. 2010).

253. While belief that a patent is invalid may negate the requisite intent for induced infringement, that belief cannot be maintained past a court's finding that a patent is valid. *Bose Corp. v. SDI Tech., Inc.*, No. 2013-1347, 2014 WL 982765 at *8 (Fed. Cir. Mar. 14, 2014).

4. Contributory Infringement

254. "Whoever offers to sell or sells within the United States or imports into the United States a component of patented . . . manufacture, combination or composition, or a material . . . for use in practicing a patented process, constituting a material part of the infringement, knowing the same to be especially made or especially adapted for use in infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use," shall be considered "a contributory infringer." 35 U.S.C. § 271(c)

255. To establish contributory infringement, the patent owner must prove that: "(1) there is direct infringement; (2) the accused infringer had knowledge of the patent at issue; (3) the component has no substantial noninfringing uses; and (4) "the component is a material part of the invention." *See Fujitsu Ltd. v. Netgear Inc.*, 620 F.3d 1321, 1326 (Fed. Cir. 2010).

256. An accused infringer's knowledge of the patents may be demonstrated by an ANDA filer's certification and Notice Letter to the patent holder. *Teva Pham. U.S.A., Inc. v. Sandoz, Inc.*, 876 F. Supp. 2d 295, 349 (S.D.N.Y 2012)

257. Only proof of a defendant's knowledge, not intent, that his activity causes infringement and knowledge of the patent which proscribes that use is required to show contributory infringement. *Hewlett–Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1469 & n. 4 (Fed.Cir.1990).

258. Contributory infringement exists where it may be presumed from distribution of an article in commerce that the distributor intended the article to be used to infringe another's patent, and so may justly be held liable for that infringement. *Metro–Goldwyn–Mayer Studios Inc. v. Grokster, Ltd.*, 545 U.S. 913, 932 (2005).

259. In assessing whether an asserted noninfringing use is substantial, a jury may consider not only the use's frequency, but also the use's practicality, the invention's intended purpose, and the intended market. *i4i Ltd. P'ship v. Microsoft Corp.*, 598 F.3d 831, 851 (Fed. Cir. 2010) *aff'd*, 131 S. Ct. 2238, 180 L. Ed. 2d 131 (U.S. 2011)

260. Non-infringing uses are substantial when they are not unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental. *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1327 (Fed. Cir. 2009)

261. Because ANDA defendants are restricted from selling a federally regulated drug for unapproved uses, prescriptions for unauthorized uses of a generic product do not avoid contributory infringement if the only authorized use of the accused infringing product is the patented use. *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 Fed. App'x 917, 927 (Fed. Cir. 2011) *citing* 21 C.F.R. § 202.1(e)(4).

262. A product is a material component of a composition when it is the sole physical object necessary to practice the method claim. *Braintree Labs, Inc. v. Novel Labs, Inc.*, 2013 WL 211252 at *13 (Jan. 18, 2013 D.N.J.).

D. CONCLUSION ON INFRINGEMENT

263. Based on the foregoing legal principles, the Court concludes that Depomed has proven by a preponderance of the evidence that the 300 mg and 600 mg ANDA Products described in Actavis' ANDA 203611 will, if produced and marketed, directly infringe claim 10 of the '989 Patent; claims 1, 2, and 5 of the '756 Patent; claims 1, 6 and 22 of the '332 Patent; and claims 1 and 5 of the '992 Patent.

264. The Court further concludes that Depomed has proven by a preponderance of the evidence that the 300 mg and 600 mg ANDA Products described in Actavis' ANDA 203611 will, if produced and marketed, induce infringement of claims 18, 25, 26, 34, 61, and 62 of the '927 Patent; claims 6, 7, and 11 of the '756 Patent; claims 17 and 24 of the '332 Patent; claim 24 of the '332 Patent; and claim 22 of the '992 Patent.

265. The Court further concludes that Depomed has proven by a preponderance of the evidence that Actavis will contributorily infringe claims 18, 25, 26, 34, 61, and 62 of the '927 Patent; claims 6, 7, and 11 of the '756 Patent; claims 17 and 24 of the '332 Patent; claim 22 of the '332 Patent; and claim 22 of

the '992 Patent if allowed to produce and market the ANDA Products described in Actavis' ANDA 203611.

VI. PROPOSED FINDINGS OF FACT – NONOBVIOUSNESS OF THE GABAPENTIN PATENTS

A. THE DEPOMED INVENTIONS ON CONTROLLED-RELEASE GABAPENTIN AS A WHOLE

266. Depomed's asserted composition and method claims are directed to a specific type of extended-release gabapentin oral dosage form that releases gabapentin in the stomach over several hours and delivers the drug in such a way that the human achieves certain blood concentrations of the drug (pharmacokinetics) and that the gabapentin has a therapeutic effect. (JTX003-007.)

267. An example of a method to treat neuropathic pain is independent claim 17 and asserted claim 18 of the '927 Patent:

> 17. A method of treating neuropathic pain in a mammal comprising administering a therapeutically effective amount of a daily dosage of about 100 mg to about 4800 mg of gabapentin or a pharmaceutically acceptable salt thereof, dispersed in a gastric retained dosage form to the mammal in which a fed mode has been induced, wherein the dosage form comprises a single polymer matrix comprising at least one swellable hydrophilic polymer that swells in a dimensionally unrestrained manner by imbibing water to increase its size to promote gastric retention of the dosage form in the stomach of the mammal, and wherein upon contact with water, gabapentin is released by diffusion from the dosage form over a period of at least five hours and at least 40 wt% of the gabapentin is retained in the dosage form one hour after administration.

> 18. The method of claim 17 wherein the dosage form is administered once-daily.

268. (JTX003 ('927 Patent), 12:38-52; ECF No. 328, Ex. 1, p. 12-13 [Stip. Fact], ¶¶ 65-66.)

269. An example of a composition is claim 1 of the '756 Patent:

> A dosage form, comprising: comprising from 100 mg to 4800 mg of therapeutically effective amount of gabapentin or pharmaceutically acceptable salt thereof, dispersed in a single matrix wherein the matrix comprises at least one swellable hydrophilic polymer that swells unrestrained dimensionally by imbibing water to increase its size to promote gastric retention of the dosage form in the stomach in a fed mode, wherein upon once-daily or twice-daily ingestion of the dosage form gabapentin is released from the matrix over a period of at least five hours wherein at least 40 wt% of the gabapentin is retained in the matrix one hour after administration, and wherein the gabapentin is released at a rate sufficient to achieve a lower maximum plasma concentration (C_{max}) compared to an equal dose of gabapentin provided by an immediate release dosage form, and without loss in bioavailability as measured by the area under the curve ($AUC_{infinity}$) as compared to the bioavailability which is achieved from an immediate release dosage form comprising the same dose of gabapentin.

An example from the last two issued patents, the '332 and the '992 Patent, is '992 Patent claim 22:

> A method of treating a condition responsive to a therapeutic dose of gabapentin, comprising:
>
> orally administering to a human subject a dosage form comprising a matrix comprising gabapentin, wherein gabapentin is released from the matrix into the upper gastrointestinal tract over about 5-12 hours at a rate sufficient to achieve a longer time to the maximum plasma concentration than that provided by an immediate release dosage form comprising an equal amount of gabapentin, and bioavailability of gabapentin is at least 80% of that provided by the immediate release

dosage form comprising an equal amount of gabapentin as measured by the area under the plasma concentration-time curve, AUCinf.

270. (JTX005 ('756 Patent), 12:50 – 13:3; JTX007 ('992 Patent), 14:13-26; ECF No. 328, Ex. 1, p. 15-20 [Stip. Fact], ¶¶ 81, 105.)

271. These claims as a whole are at the intersection of the disciplines of (1) extended-release formulation, (2) gastric retention/gastroenterology, (3) pharmacokinetics, (4) pharmacodynamics, and (5) gabapentin as reflected in the different types of experts that testified at trial.

272. Key elements of the claims considered as a whole include:

a. The dosage form is a matrix or single polymeric matrix;

b. The dosage form is specific for the controlled-release of gabapentin;

c. The claimed controlled-release gabapentin dosage form must achieve *in vivo* certain pharmacokinetic parameters of (i) lower C_{max} compared to IR Gabapentin, (ii) extended T_{max} as compared to IR gabapentin and/or (iii) at least 80% AUC as compared to the same dose of IR gabapentin;

d. The controlled-release dosage form must in fact remain in the stomach for several hours;

e. The controlled-release dosage form must swell *in vivo*;

f. The dosage form for many of the claims must release by diffusion.

273. Gabapentin immediate release was approved for sale in 1993 under the trade name Neurontin and is administered three times per day. ECF No. 328,

Ex. 1, p. 22 [Stip. Fact], ¶ 119. (Trial Tr. (Bockbrader), 751:3-5; Trial Tr. (Gidal), 818:9-25; Trial Tr. (Brown), 871:6-15.)

274. Neurontin became a blockbuster drug product by the late 1990s. (Trial Tr. (Bockbrader), 772:6-11; Trial Tr. (Felton), 975:25 – 976:4; Trial Tr. (Nicholson), 1067:24 – 1068:14.)

275. Depomed's Gralise product, approved by the FDA in 2011, is the first and only gabapentin extended-release dosage form that may be marketed in the United States. ECF No. 328, Ex. 1, p. 20-21 [Stip. Fact], ¶¶ 106-108, 110.

276. The priority date of the Depomed gabapentin patents ('927, '989, '756, '332 and '992 Patents) is October 25, 2001. (JTX003 ('927 Patent), at p. 1 (issued from application no. 10/280,309); JTX004 ('989 Patent), at p. 1, "Related U.S. Application Data" (issued from continuation of application no. 10/280, 309 and claiming priority to provisional application no. 60/335,248 filed October 25, 2001); JTX005 ('756 Patent), at p. 1, "Related U.S. Application Data" (claiming priority to provisional application no. 60/335,248 filed October 25, 2001); JTX006 ('332 Patent), at p. 1, "Related U.S. Application Data" (same); JTX007 ('992 Patent), at p. 1, "Related U.S. Application Data" (same).)

B. THE PERSON OF ORDINARY SKILL IN THE ART

277. Actavis's expert, Dr. Flanagan testified that a person of ordinary skill in the art is a person with a Ph.D. in chemistry, chemical engineering,

pharmaceutical sciences, or a related discipline. Alternatively, the person could have a master's degree in one of those fields, with at least two years of practical experience and alternatively, the person could have a Bachelor's degree in one of those fields with even more practical experience. (Trial Tr. (Flanagan), 553:13-24.)

278. Depomed's experts said that a person of ordinary skill in the art in the field of the asserted patent claims would have a formal education or at least a Bachelor's degree in the fields of chemistry, chemical engineering, and/or pharmaceutical science and/or material science, with a focus on polymer science, combined with substantial experience in development of controlled-release dosage forms. Moreover, for the elements in the patent claims that address pharmacokinetics, gastric retention and/or treatment-related limitations, such person would have a formal education and/or experience relevant to those areas. Alternatively, if the person had obtained a Ph.D. in any of those relevant fields, the required amount of industry experience would decline to about two years. (Trial Tr. (Hopfenberg), 932:6-25; Trial Tr. (Felton), 960:6 – 961:6; Trial Tr. (Flanagan), 554:6-23.)

279. Dr. Flanagan testified that his opinion would not change if he had applied Depomed's definition of person of ordinary skill in the art. (Trial Tr. (Flanagan), 554:24 – 555:1.)

C. THE SCOPE AND CONTENT OF THE PRIOR ART

1. It Is Undisputed That Challenges Existed to Creating an Effective Extended-release Gabapentin Formulation

280. The unique characteristics of gabapentin posed several challenges to one of skill in the art who wanted to create an extended-release formulation of gabapentin. (Trial Tr. (Felton), 964:2-8.)

a. Ensuring That Gabapentin was Available for Absorption at the Correct Site was Challenging

281. The first challenge was to ensure that the drug was available for absorption. (Trial Tr. (Felton), 964:10-25.)

282. It is undisputed that gabapentin has a narrow window of absorption. (Trial Tr. (Flanagan), 560:6-8; (Felton), 983:12-17; (Gidal), 828:16 – 829:5.)

283. Actavis's expert Dr. Flanagan testified that the window of absorption was an important characteristic for a formulator developing a controlled-release dosage form. Dr. Flanagan testified that "[i]f the drug is only absorbed in a certain region of the GI tract, then one has to develop a formulation that will release it in the region where it will be absorbed." (Trial Tr. (Flanagan), 564:13-17.)

284. The poor absorption of gabapentin and its restricted area of absorption posed challenges in designing an effective controlled-release formulation. (Trial Tr. (Gidal), 853:8-16.) For example, Rebeccah Collins and William Garnett explained the drawbacks of formulating gabapentin in a controlled-release formulation in light of gabapentin's saturable transport, narrow window of

absorption, and 5 to 7 hour half-life in the blood. (Trial Tr. (Gidal), 853:21-854:13.)

> Gabapentin has a half-life of 5 to 7 hours and requires an administration interval of 8 hours; however, it is absorbed by an L-amino acid carrier system that may not be present throughout the gastrointestinal tract and which may be saturable. These characteristics would limit the use of an ER formulation.

(Collins et al. (2000) (PTX000501) at 205 (GRALISE_JDG_00000975) (citation omitted).)

> To date, efforts to develop a sustained release formulation of gabapentin have failed, primarily due to the lack of significant absorption of the drug in the large intestine (Kriel et al., 1997).

(Cundy et al. (2004) PTX000269 at 316 (DEPOACT0958153).)

285. Because the drug is absorbed in the upper regions of the gastrointestinal tract (small intestines), the drug would need to be released at that site or above in order to be absorbed into the body. "There are potentially two general approaches to achieve that drug release in the right location in the body. The first would have been to slow intestinal motility of the dosage form in the small intestines. But it is probably not a good idea to have to take one medication in order to get a second medication absorbed." The second alternative was a gastro-retentive system, of which there are many possibilities. (Trial Tr. (Felton), 964:10 – 965:17, 957:21 – 969:8.)

286. These two approaches are described in the literature. The art of gastric retained dosage forms was an emerging art in 2001 as explained in the 1998 *Hwang* reference. (Trial Tr. (Felton), 968:15-21.)

> "Thus, the real issue in the development of oral controlled-release dosage forms is how to extend the time for drug absorption from the small intestine. For example, oral dosage forms may have to stay in the stomach or somewhere in the upper small intestine until all the drug is released for desired periods of time. Designing platforms that target the upper small intestine is rather difficult, since they would have to be an adhesive-type system that selectively adheres to the jejunum or ileum surfaces. Carbohydrate-containing copolymers[3,4] and lectins[5-11] have been tried in order to target selective sites in the intestine. These approaches are highly promising and are expected to become practical once there is further understanding of the specific ligands present in the intestine. Currently, however, it is rather difficult to place oral dosage forms at selected sites in the small intestine. For this reason, most research efforts have been focused on platforms to extend gastric residence time.

(*Hwang* 1998 (DTX00222) (GRALISE_JDG_00000385).)

> Methods designed to provide longer contact of the drug or delivery system with the crucial absorption region fall into two different categories: (i) those that attempt to slow down transit through the small intestine; and (ii) those that attempt to hold the drug formulation above the absorption window through gastric retention.

(*Davis* 2005 (PTX000274) (DEPOACT0970223).)

b. Ensuring That Gabapentin Was Released at a Slow Enough Rate To Avoid Saturating the Transporters, but yet High Enough to be Therapeutically Effective was Challenging

287. Another challenge was gabapentin pharmacokinetics and bioavailability. (Trial Tr. (Felton), 966:4-10.)

288. Actavis's expert Dr. Flanagan testified that saturable absorption was another important characteristic for a formulator making controlled-release dosage form. Dr. Flanagan explained if the gastrointestinal tract has some limitation on how much of a drug that can be absorbed, that drug needs to be formulated so that it releases at a slow enough rate to be efficiently absorbed without saturating the absorption system. (Trial Tr. (Flanagan), 563:8-16.)

289. It is undisputed that gabapentin is absorbed only in the upper gastrointestinal tract by saturable transporters. (Trial Tr. (Bockbrader), 748:20 – 749:3; (Flanagan), 563:8-16.)

290. Bockbrader and others reported for the first time in 1995 that gabapentin was saturably absorbed by L-amino acid type transporters. (Trial Tr. (Bockbrader), 747:9 – 748:7; PTX000271.)

291. A formulator would need to ensure that the drug release occurs at a rate that will not saturate the transporters, but be high enough to achieve therapeutically meaningful blood levels. (Trial Tr. (Felton), 966:4-10.)

292. Thus, not only must the dosage form be gastric retained, it must also release the drug in a controlled manner to ensure slow release of the drug that does not saturate the transporters and further results in therapeutically meaningful levels of gabapentin in blood. (FOF 280-291.)

293. Further, as Dr. Bockbrader explained, gabapentin's half-life of about 6 hours meant that if a single dose per day was administered, absorption would need to be maintained over an extended period of time as the half-life in the blood would be short. Effectively, after 10-12 hours with no absorption, 75% of gabapentin would be eliminated. (Trial Tr. (Bockbrader), 759:4-7, 758:7-13.)

294. No information was available on the capacity of the transporters for gabapentin or affinity of the transporters for gabapentin, which could provide information about absorption kinetics of gabapentin. (Trial Tr. (Derendorf), 1043:12-19, 1044:21-22.)

295. There was also no target pharmacokinetic profile to aim for. One could aim to achieve a pharmacokinetic profile identical to that from an immediate release gabapentin dosage form used in treatment of PHN. "If you could achieve that exactly the same profile, then you would expect the same outcome, yes"—therapeutic efficacy. However, "most likely with the controlled-release product, you will get a different kind of profile that you will then need to show either by modeling with no PK PD relationship or by clinical study that it will work." (Trial Tr. (Derendorf), 1048:16 – 1049:16.)

296. "[I]f you don't have a PK/PD relationship, you don't have a target. You don't know how the exposure is linked to the response." (Trial Tr. (Derendorf), 1033:10-14.)

297. It is undisputed that gabapentin does not have a known PK/PD relationship. (Trial Tr. (Derendorf), 1029:19-22.)

298. Thus, without a known PK-PD relationship for gabapentin, there would not be a target profile to aim for that would guarantee therapeutic efficacy. Additional clinical studies would need to be conducted to prove that the product works. (Trial Tr. (Derendorf), 1033:15-21.)

c. Ensuring That Gabapentin Does Not Degrade to Toxic Lactam was a Challenge

299. Another challenge was gabapentin's degradation into lactam. For any drug that degrades in an acidic environment such as in the stomach, that means the drug will be degrading and there will be less drug that could be absorbed for its therapeutic effect. With gabapentin in particular, it is a drug that can not only degrade in acidic environment, but can degrade to a toxic product, lactam. (Trial Tr. (Felton), 965:18 – 966:3; Trial Tr. (Gidal), 855:7-16, 856:7-14.)

300. Gabapentin degrades slowly into lactam as a function of pH, temperature and buffers which can accelerate some of this process. (Trial Tr. (Gidal), 856:1-3; PTX000290.)

d. Ensuring That the Dosage Form was Safe — Avoiding Gastrointestinal Blockage Was a Challenge

301. An additional challenge was a safe dosage form. In addition to the issue of toxic lactam formation, the gastroretentive system that's designed to stay

in the stomach for an extended time frame, must not lodge in the stomach and cause discomfort to the patient. (Trial Tr. (Felton), 966:12-19.)

302. For example, the 2005 *Davis* reference notes that the gastric retentive system must be retained in a safe and reliable manner. "It must not swell or expand in the oesophagus or in the intestines, if it emptied prematurely from the stomach (e.g. problems could arise from the formation of an insoluble mass known as bezoar)." (*Davis* 2005 (PTX000274) at DEPOACT0970226.)

e. Uncertainty That an Extended-release Gabapentin Dosage Form Would Be Therapeutically Effective

303. The fifth challenge was ensuring a therapeutically effective amount of the drug gets into the body to exert its therapeutic effect. (Trial Tr. (Felton), 966:20 – 967:1.)

304. It is undisputed that the amount of gabapentin in blood that was necessary to mediate its therapeutic effect was unknown. (Trial Tr. (Gidal), 842:15 – 843:15, 844:20 -846:15.)

305. Information about therapeutic efficacy of Neurontin cannot be translated to that an extended-release gabapentin formulation. (Trial Tr. (Gidal), 842:21 – 843:15.)

306. Finally, further uncertainties posed additional challenges to the drug formulator seeking to create a controlled-release gabapentin formulation. Gabapentin absorption is known to vary depending on the food types that someone

consumes and gabapentin absorption is also known to vary amongst different patients. (Trial Tr. (Felton), 967:2-10.)

307. Dr. Gidal explained that the pharmacokinetics of gabapentin were not straightforward, but were unpredictable. When a drug exhibits linear absorption, one can predict how much drug is going to get in when a dose of the drug is given. That is not true with the saturable absorption seen with gabapentin. Further, there was inter-person variability in the absorption of gabapentin. If a dose of gabapentin is given to everyone in the courtroom, one cannot predict the level of drug in blood in an individual. Furthermore, there were potential food effects on gabapentin absorption. Finally, the mechanism underlying all these variables is unknown. There is likely a genetic mechanism, but it is unclear. Dr. Gidal concluded that for all these reasons, he was skeptical that an effective controlled-release gabapentin formulation could be crafted. (Trial Tr. (Gidal), 817:8 – 818:1.)

2. The Art of Creating an Effective and Safe Gastric Retained Dosage Forms Was Emerging in 2001

a. No FDA Approved Gastric Retentive Devices Were Available in the Marketplace in 2001

308. It is undisputed that no FDA approved gastric retained dosage forms were available in the market place in 2001. (Trial Tr. (Flanagan) 663:8-12.)

309. In the late 1990's and early 2000's, the gastro-retentive drug delivery approach was an emerging art and was not well-developed. There are surveys of

possible gastric retention systems described in the literature. (Trial Tr. (Felton), – 971:21; *Hwang* 1998 (DTX00222).)

b. The 1998 *Hwang* Reference Describes Multiple Potential Approaches to Gastric Retention of Dosage Forms, but Notes Lack of Gastric Retentive Device for Human Application

310. The *Hwang* reference was identified by Actavis and relied upon by Dr. Flanagan in his expert report. (Trial Tr. (Flanagan), 654:20-655:1.)

311. Dr. Flanagan admitted that the *Hwang* reference was published in 1998 and forms part of the state of the art as of October 2001. (Trial Tr. (Flanagan), 655:2-8.)

312. The reference provides a comprehensive view of the state of art as of 1998. (Trial Tr. (Hopfenberg), 945:23 – 946:10.)

313. In 1998, no long-term gastric retention device was available, and a need for such a device was expressed in the *Hwang* paper. (Trial Tr. (Hopfenberg), 948:3-17; *Hwang* 1998 (DTX00222).)

314. The *Hwang* reference describes several possible approaches to gastro-retentive drug delivery system. (Trial Tr. (Flanagan), 656:9-11.)

315. The several possible approaches to develop gastric retentive devices include: (1) gas generating floating systems; (2) low density core systems; (3) high density systems; (4) mucoadhesive systems; (5) magnetic systems; (6) unfoldable, extendible or expandable systems, including systems extending to complex

geometric shapes and larger sizes; (7) superporous hydrogel systems (Trial Tr. (Flanagan), 661:13-662:9; *Hwang* 1998 (DTX00222) (GRALISE_JDG_00000396-415).)

316. The *Hwang* reference concludes by saying that it is unclear whether a gastric retentions device is "truly working or not" and "[w]e have great hope that a long-term gastric retention device for human application will be developed in the near future." (*Hwang* 1998 (DTX00222) (GRALISE_JDG_00000417 and GRALISE_JDG_00000418); Trial Tr. (Hopfenberg), 948:3-17.)

317. *Hwang* states, for example:

> VI. OPTIMIZATION OF GASTRIC RETENTION DEVICES FOR HUMAN APPLICATIONS
>
> The literature is full of conflicting information. Gastric retention devices that work in one laboratory often prove not to work in others. When a proposed gastric retention device does not work, the immediate conclusion drawn by the study is obviously that the system does not work. As we reviewed the literature, we have noticed a few things. First of all, no study has been done comprehensively to conclude whether any gastric retention device is truly working or not. Most of the studies that showed that a proposed system did not work were often based on inadequate controls and an inadequate number of volunteers. While the studies may have produced negative results, these results were hardly sufficient to conclude that the system did not work.
>
> * * *
>
> "The lesson here is that there's too much variation in human volunteers, *unrealistic to derive any conclusion from advanced retention study involving only a handful of human volunteers*."

* * *

> We have great hope that a long-term gastric retention device for human application will be developed in the near future. As presented here, each gastric retention system approach has its own unique concept and each requires further improvements to be effective. Progress will only be possible if all the researchers in the field work together to analyze a concept, test it, and find ways to overcome limitations. Only after we accomplish long-term gastric retention devices can the full benefits of controlled-release technologies be realized for oral controlled-release dosage forms.

(*Hwang* 1998 (DTX00222) at GRALISE_JDG_0000417-18.)

c. Still No Clear Indication by 2005 That a Particular Approach Would Be Effective in Gastric Retention

318. The 2005 *Davis* reference recognizes challenges with formulating drugs with narrow window of absorption into extended-release formulation. The paper identifies gabapentin as one of those drugs. (*Davis* 2005 (PTX000274) at DEPOACT0970223.)

319. The paper describes gastric retention as simple and elegant in theory, and the subject of "extensive research, publications, and patent filings, with some successes, but many failures." The paper notes that approaches promising in vitro or in animals have not always translated well in humans. The paper states:

> **Gastric retention**
>
> In theory, an elegant and simple way to improve drug absorption is to hold a drug delivery system above the absorption window and for the drug to be released at an appropriate rate. Because most absorption windows are thought to be located in the proximal small intestine, the obvious strategy will be to hold the formulation in the stomach (i.e. gastric retention). This concept was advanced many years ago and

> has been the subject of extensive research, publications and patents filings, with some successes, but many failures. The Holy Grail remains the retention of a delivery system in the fasting human stomach using a system that will be safe and effective.
>
> * * *
>
> Attention will be focused on systems that have been tested in humans. As discussed earlier, promising results obtained *in vitro* and in animal models have not always translated well to human.

(*Davis* 2005 (PTX000274) at DEPOACT0970225.)

320. Among the different approaches for gastric retention, the 2005 *Davis* paper identifies swelling and expanding systems as the most promising, but notes that many approaches are encompassed within the swelling and expanding system, including gas generating systems, hydrogels, and unfolding structures. (*Davis* 2005 (PTX000274) at DEPOACT0970226-0970228.)

321. The 2005 *Davis* reference concludes that a "swelling or expanding system appears to be the best option, but rapid change in dimensions will have to be achieved in a fail-safe manner. Furthermore, the system will need to retain its integrity for an extended period of time in the harsh conditions present in the human stomach." (*Davis* 2005 (PTX000274) atDEPOACT0970228.)

d. Even by 2012, Success With Gastroretentive Devices was Limited as Demonstrated in the Lalloo Paper and Required *In Vivo* Data to Understand if the Functionality Was Achieved

322. Even by 2012, success with gastric retention strategy was limited. Many of the gastric retention "technologies have not translated into clinically-

acceptable products, although some success has been demonstrated with Glumetza, with Proquin XR and Gralise, all of which exhibit some degree of gastric retention when administered in the fed state." (Hopfenberg 949:12 – 950:1; Lalloo (PTX000488) at DEPOACT0981945.)

323. None of Glumetza, Proquin XR or Gralise was marketed in 2001. Glumetza, Proquin XR and Gralise are Depomed products. Glumetza and Proquin XR were approved by the FDA in 2005, and Gralise in 2011. (Hopfenberg, 950:2-19.)

324. "A critical design feture of GR formulations is the ability to withstand strong contraction forces in the stomach. . . . Imaging data is valuable in determining whether a formulation is retained in the stomach or prematurely released into the small intestine; however, achieving the desired pharmacokinetic profile demonstrates true success of a GR formulation." (Lalloo (PTX000488) at DEPOACT0981953.)

325. "Well, it's clear that Lalloo and co-workers understand that *in vivo* data is important, as well as *in vitro* data, to understand the functionality of [a] gastrically-retained dosage form." (Trial Tr. (Hopfenberg), 951:3-6.)

3. No Specific Motivation Existed To Make an Effective Extended-Release Gabapentin Dosage Form Despite Potential Advantages From Once-Daily Dosing and Reduced Side Effects

a. No Specific Motivation Existed To Make a Gabapentin Extended-Release Formulation Because Simulating Slow Release Did Not Predictably Decrease Transporter Saturation Problem

326. Dr. Gidal testified that recognizing that gabapentin is absorbed by a saturable mechanism, he and others in his laboratory hypothesized that if they gave the same daily dose of the drug but gave it more frequently, such as to simulate slowly releasing controlled-release dosage form, the bioavailability of drug would improve and more of the drug would get absorbed. (Trial Tr. (Gidal), 819:15 – 820:6.)

327. Because a controlled-release formulation would not deliver the entire payload at once, saturation of gabapentin absorption was not a problem, but reducing saturation would instead motivate one to make an extended-release dosage form of the drug. (Trial Tr. (Derendorf), 364:10-15; Trial Tr. (Felton), 1010:8-12.)

328. However, Dr. Gidal's studies provided unexpected results. Bioavailability improved with patients who were given a 4800 mg/day dose of gabapentin but not a 3600 mg/day dose of gabapentin. (Trial Tr. (Gidal), 820:7 – 822:10.)

329. Dr. Gidal concluded that the strategy of simulating a slower delivery of the drug to overcome the saturation problem did not work at the lower dose as they thought it might. It was an unexpected finding. (Trial Tr. (Gidal), 823:12-25.)

330. These results were published in 1998 in Gabapentin Bioavailability: Effect of Dose and Frequency of Administration in Adult Patients With Epilepsy, Gidal et al., EPILEPSY RESEARCH 31 (1998) 91-99. (See PTX000502.)

331. Actavis does not dispute the data or the results of the study that one of skill would have been aware of and been skeptical that extended-release could avoid saturation.

b. No Specific Motivation Existed To Make a Gastric Retained Gabapentin Dosage Form Because the Stomach Environment was Thought to Accelerate Degradation of Gabapentin to a Toxic Lactam By-Product

332. *Hwang* describes that certain drugs are not suitable for gastric retentive systems. *Hwang* provides "it goes without saying that drugs unstable in the acidic pH of the stomach cannot be used in gastric retentive devices." (*Hwang* 1998 (DTX00222) at GRALISE_JDG_00000387.) "Gabapentin is a drug that was known to degrade in the presence of acid more quickly to a toxic lactam." (Trial Tr. (Felton), 971:22 – 972:19; *see* 972:18-19)

333. Dr. Felton therefore testified that based on *Hwang*, it would "not be a good idea" to put gabapentin in a gastric retained delivery system. (Trial Tr. (Felton), 972:20 – 973:3)

334. Dr. Felton further testified that other references also support her opinion that one of skill in the art would not be motivated to put gabapentin in a dosage form exposed to stomach environment. Dr. Felton explained that other references also "demonstrate that the drug does degrade to a lactam, a toxic component, and the rate at which that degradation happens is going to be dependent on what people have consumed or what's is in their stomach, whether there's buffer, what the pH is." (Trial Tr. (Felton), 998:24 – 1001:3; *see* 1000:24 – 1001:3.)

335. There is no evidence that swellable polymers *per se* protect drugs from the gastric fluid. (Trial Tr. (Felton), 1009:15-17.) In fact, the identity of ingredients that enhance lactam formation follows no recognizable logic. (*See* PTX000361, 4:58-64) ("in the case of investigations of final pharmaceutical forms, it was found, as a further problem, *that the cause of the lactam formation was apparently also the catalytic effects of adjuvant materials which also did not follow any recognizable logic.* In order to establish which adjuvant materials promote the lactam formation, laborious serial investigations had, therefore, to be carried out.") (emphasis added). Even further, as Dr. Felton testified in rebuttal testimony, food

and other excipients in the stomach could also accelerate the formation of lactam. (Trial Tr. (Felton), 998:24 – 1001:3.)

336. Based on teachings of *Hwang* and other references, which teach that a drug unstable in acidic pH of the stomach is unsuitable for a gastric retentive devices, and gabapentin degrades more quickly to toxic lactam in the presence of an acid, a person of ordinary skill in the art would not have a reasonable expectation of success if they put gabapentin in a gastric retained dosage form. (Trial Tr. (Felton), 972:8 – 973:7)

337. Likewise, Dr. Gidal testified that because of the concern that an acidic environment could facilitate the lactam formation, a drug that stays in the stomach for a long period would be a concern that this could lead to the toxic lactam formation. (Trial Tr. (Gidal), 856:7-14.)

338. WO ‘755 (DTX00230) is not to the contrary. That reference states, without experimental support, that its disclosed dosage forms can protect acid-labile peptides, proteins, or proton pump inhibitors from gastric fluid. (DTX00230 (WO ‘755) at 4:24 – 5:4 (GRALISE_JDG_00000902 – GRALISE_JDG_ 00000903).) However, WO ‘755 teaches drug/polymer mixtures in the form of a “plurality of particles” that are delivered to the stomach in a “tablet or capsule [which] rapidly disintegrates in the gastric fluid to permit the particles to disperse in the stomach. (*Id.* at 2:32-36 (GRALISE_JDG_00000900) & 7:30-31

(GRALISE_JDG_00000905).) In constrast to the inventions of the Gabapentin Patents, which require the use of the highly soluble drug gabapentin, WO '755 is directed to the formulation of dosage forms for drugs with "limited solubility." (*Compare id.* at 3:6-8 (GRALISE_JDG_00000901) *with, e.g.,* JTX003 ('927 Patent), 2:17-21 & 2:30-35.) The release of these low solubility drugs from a matrix is controlled by their rate of dissolution whereas the Gabapentin Patents release drug primarily by diffusion. (*Compare* DTX00230 (WO '755), at 7:2-6 (GRALISE_JDG_00000905) *with* JTX003 ('927 Patent), 12:48-49; *see also* Trial Tr. (Williams), 264:8 – 265:19.) Thus, very different release-controlling mechanisms are contemplated in WO '755, as compared with the diffusion-controlled-release mechanism disclosed and claimed in the Gabapentin Patents.

339. There is no evidence that the person of ordinary skill in the art would look to WO '755 for teaching on how to protect gabapentin from the acidic environment of the stomach. (Trial Tr. (Felton), 1007:22 – 1009:20.)

c. No Specific Motivation Existed To Make an Extended-release Gabapentin Dosage Form That Is Dependent on Food Because Food Has a Variable Effect on Gabapentin Absorption

340. Food has a variable effect on gabapentin absorption. Studies from Dr. Gidal's laboratory and others have indicated that food has a variable effect on gabapentin absorption. Because both gabapentin and certain amino acids are transported by the same transporter, "System L," it was hypothesized that, in the

presence of a protein rich diet, gabapentin absorption would be reduced because the amino acids in the protein would compete with gabapentin for transport. (Trial Tr. (Gidal), 829:21-831:8.)

341. Unexpectedly, however, the presence of a protein rich diet *enhanced* the bioavailability of gabapentin. (Trial Tr. (Gidal), 831:8-24; (Barry E. Gidal et al., *Effect of a High-Protein Meal on Gabapentin Pharmacokinetics*, 23 EPILEPSY RESEARCH 71, 74 (1996), (hereinafter "Gidal et al. (1996)"). (PTX000276 at DEPOACT0970241.)

342. To further understand food effects, Dr. Gidal evaluated gabapentin absorption following a diet of Neurontin mixed with water, apple sauce, orange juice or chocolate pudding. (Trial Tr. (Gidal), 832:18 – 834:8; (Barry E. Gidal et al., *Gabapentin Absorption: Effect of Mixing with Foods of Varying Macronutrient Composition*, 32 THE ANNALS OF PHARMACOTHERAPY 405 (1998), (hereinafter "Gidal et al. (1998-2)"). (PTX000270 at DEPOACT0958992.) The data from the study suggested that food composition, particularly protein, could influence gabapentin absorption. (*Id*.)

343. In light of the variability in gabapentin absorption in the presence of food, one would not be motivated to choose a dosage form, whose therapeutic mechanism of action depends upon food. (Trial Tr. (Gidal), 834:19 – 835:20; (Felton), 962:21 – 963:1, 967:4-10, 975:5-9.)

344. In a book chapter published in 2002, Actavis expert Dr. Michael Mayersohn discussed the then-state of the art thinking about how food impacts drug absorption. (Trial Tr. (Mayersohn), 737:7-15, 738:5 – 740:11.) Statements authored by Dr. Mayersohn in that chapter reflect his opinions in 2000-2001. (*Id.* at 738:5-14, 738:25 –740:11.)

345. Dr. Mayersohn discussed his survey of the scientific literature as of 2000-2001 and wrote in regard to food effects on drug absorption:

> Several recent publications have reviewed the effects of food on drug absorption in humans [70-72]. **The effect of food on the gastrointestinal absorption of drugs is complex and multidimensional. We are only now beginning to understand this complexity. The physical presence of food in the GIT may play a significant role-in affecting the efficient absorption of a drug from an oral dosage form. The ultimate effect of food on the rate and/or extent of gastrointestinal absorption is a function of numerous interacting variables**. While some general rules may be postulated, the effect of food on a given drug and its dosage form will require, in general, individual investigation. The U.S. Food and Drug Administration (FDA) has recognized this complexity and requires that all dosage forms that do not immediately release drug (e.g., controlled-release formulations) undergo a food-effects study in humans, for which a "Guidance" has been written (these are available on the FDA webpage-fda.gov).

346. (PTX000521 at DEPOACT0982013 (emphasis added); Trial Tr. (Mayersohn), 738:15 – 739:22.)

347. Dr. Mayersohn also discussed the variables that one of skill in the art in 2000-2001 must consider in regard to the food effects on drug absorption:

> **The extent to which food will alter absorption depends upon factors such as physical chemical characteristics of the drug (e.g., aqueous solubility, oil/water partition coefficient, and stability in gut fluids), the dose of drug, the characteristics of the dosage form, time of drug administration relative to food ingestion, amount of food, and type of food**. The schematic in Fig. 11 summarizes the variables that food is able to affect, which in turn are associated with the sequential steps of drug release, dissolution, absorption, systemic availability, and elimination. Notice the two heavy arrows for the dissolution and absorption steps. One of those two processes is generally associated with the rate-limiting step in the overall absorption of a. drug. Therefore, when food affects drug absorption, it most often does so by affecting the factors influencing dissolution or transport. Most of the factors noted in Fig. 11 are self-explanatory, but many will be discussed with examples in the following sections.

348. (PTX000521 at DEPOACT0982013 (emphasis added); Trial Tr. (Mayersohn), 739:23 – 740:11.)

349. Later in his 2002 book chaper, Dr. Mayersohn addressed food transit through the small intestine and concluded that food does not impact the intestinal transit of food as it does stomach emptying:

> **Transit through the small intestine appears to be quite different in a variety of ways from movement through the stomach. Once emptied from the stomach, material (such as pellets and tablets) will move along the small intestine and reach the ileocecal valve in about 3 hours.** While this value may range from about 1 to 6 hours, intestinal residence time appears to be relatively consistent among normal subjects [87]. Values similar to this have been found for food and water movement along the small intestine. Transit appears to be less dependent upon the physical nature of the material (liquid vs. solid and size of solids) compared to the response of the stomach. **Further, food appears not to influence intestinal transit as it does gastric emptying.**

350. (PTX000521 at DEPOACT0982017 (emphasis added); Trial Tr. (Mayersohn), 740:12 – 741:1.)

351. The ileocecal valve is the valve at the lower end of the ileum region at the end of the small intestines. (Trial Tr. (Mayersohn), 741:2-11.)

352. In 2002, gabapentin would have been expected to have minimal if not non-existent absorption in the small intestine. (Trial Tr. (Mayersohn), 741:7-25.)

353. Actavis suggests that food effects were not clinically significant for Neurontin, and that the Neurontin label provides that Neurontin could be taken with or without food. (Trial Tr. (Felton), 1010:25 – 1011:9.)

354. However, unlike Neurontin, which need not be taken with food, the WO '107 dosage form and the WO '128 dosage form are described to be taken with food. Given the food effect, a skilled artisan would at a minimum have tried to minimize the food effect by searching for a dosage form that, like Neurontin, was not dependent on food.

4. No Reasonable Expectation of Success That a Controlled-release Gabapentin Formulation Would Be Absorbed Into the Blood Stream Because Gabapentin Absorption is Known to Vary Based on the Individual, the Dose and Food Intake

355. Studies conducted by Dr. Gidal and others indicated that there was significant variability in gabapentin absorption between persons. This variability

was seen with patients (Trial Tr. (Gidal), 823:12-25; PTX000502) and normal subjects. (Trial Tr. (Gidal), 824:9-15.)

356. The results of the study with normal subjects were published in 2000 in Inter- and Intra-subject variability in gabapentin absorption and absolute bioavailability, Gidal et al., Epilepsy Research 40 (2000) 123-127 (PTX000275)

> The results of the present studies do highlight the point that the use of 'average' population kinetic data may be misleading in situations where substantial variability exists. In other words, although the average variabiilty of a 600 mg oral dose of gabapentin was 49%, individual subjects may vary greatly (5-74%). The clinical implication is that 'typical' or 'usual' doses are likely to result in quite different plasma concentration in individual patients. Indeed, similar observations were noted by Beydoun et al. in an efficacy trial of gabapentin monotherapy.

(PTX000275 (DEPOACT0970237).) As Dr. Gidal noted, inter-person variability in absorption of gabapentin ranged from 5 to 74%.

357. Actavis's expert Dr. Mayersohn acknowledged the inter-person variability noting that the variability was three fold even after excluding "outliers." (Trial Tr. (Mayersohn), 735:1-5; 735:21 – 736:6.)

358. In response to Dr. Mayersohn's testimony, Dr. Gidal explained he does not discard such data because the experiment and data are valid. "By discarding it as inconvenient to us, I think we're discarding some biology here. There's something about that individual we just don't know what it is." Dr. Gidal further noted that there were several individuals who showed less bioavailability of

gabapentin than that suggested by the product information, indicating that the inter-subject variability in gabapentin absorption is a big spread. (Trial Tr. (Gidal), 825:25 – 826:13.)

359. This is consistent with Dr. Gidal's testimony that he was skeptical that a controlled-release gabapentin would not be therapeutically effective.

360. Dr. Gidal concluded that the inter-subject variability in gabapentin absorption caused him to be skeptical that an extended-release gabapentin dosage form that is consistently absorbed across a population could be made. (Trial Tr. (Gidal), 826:14-21; 827:18-22.)

361. Actavis suggests that variability in gabapentin absorption would not be a problem for after all variable absorption never stopped sales of Neurontin. (Trial Tr. (Felton), 1010:15-24.)

362. Yet, Actavis's expert, Dr. Sinatra, explained that Neurontin is ineffective in many patients (Trial Tr. (Sinatra), 898:22 – 899:10), suggesting that inter-person variability in gabapentin absorption likely had therapeutic consequences.

D. THE WO '107 PRIMARY REFERENCE TOGETHER WITH OTHER REFERENCES DOES NOT RENDER THE ASSERTED CLAIMS OF THE '927, '989, '756, '332 AND '992 PATENTS OBVIOUS

1. Summary of References

363. Dr. Flanagan testified that the asserted claims of the '927, '989, '756, '332 and '992 Patents are rendered obvious by the primary reference WO '107 patent application (DTX00234) ("WO '107 Reference"), along with Rowbotham, M. et al., Gabapentin for the treatment of postherpetic neuralgia: randomized controlled trial, 280(21) JAMA 1837-42 (1998) (DTX00313)("Rowbotham") and McLean, M.J. Gabapentin, 36 (Supp. 2) EPILEPSIA S73-S86 (1995), and knowledge of one of ordinary skill in the art. (Trial Tr. (Flanagan), 638:12-22; 639:7-10.)

364. Dr. Flanagan testified that knowledge of one of skill in the art would be provided by Applied Biopharmaceutics & Pharmacokinetics (2d. Ed. 1985) (DTX00323) ("AB&P"), 21 CFR § 320 (DTX00005), WO '128 patent application (DTX00236) (" WO '128 reference") and the Neurontin Label (DTX00291).

a. WO '107 Does Not Disclose Swelling Data, *In Vivo* Data, Pharmacokinetics or Gabapentin

365. WO '107 is directed at dosage forms for gastro-retention and the *in vitro* release examples that are cited are Metformin hydrochloride, Captopril and Vancomycin." (Trial Tr. (Felton), 973:22-24.) Gabapentin is not cited as a possible drug to be used in WO '107.

366. WO '107 discusses gastro-retentive systems "to treat local conditions in the stomach as well as to provide control release for drugs that are absorbed from a narrow window of absorption." (Trial Tr. (Felton), 973:8-974:3)

367. No in vivo pharmacokinetic data for any drug is provided in the '107 reference for any drug and no *in vitro* drug release data for gabapentin is provided in the '107 reference. (Trial Tr. (Felton), 974:4-15)

368. As the WO '107 Abstract acknowledges, the release characteristics are tied to the swelling of the dosage form. No swelling data or studies are disclosed in WO '107.

369. No data is disclosed in WO '107 that the dosage form swells to a size that achieves gastric retention.

b. McLean I & Rowbotham Disclose Only Immediate Release Gabapentin

370. The references disclose that "gabapentin is absorbed by the L amino transporter system and that the bio-availability is not dose proportional, likely related to the saturable absorption kinetics" and that potential therapeutic uses for gabapentin include "seizures and neuropathic pain." (Trial Tr. (Felton), 982:5-13.)

371. "[T]here is no discussion about extended-release dosage forms or even the suitability of gabapentin to be put in an extended-release dosage form," but are devoted solely to the immediate release form of the dosage form. (Trial Tr. (Felton), 982:14-22; (Flanagan), 619:15-17.)

c. AB&P & 21 CFR 320 Are General References That Teach a Goal of Extended-release but Do Not Teach How To Make Such a Formulation, as Dr. Flanagan Admitted

372. 21 CFR 320 and AB&P are "general references. They do not discuss gabapentin" or teach "gabapentin or gabapentin bioavailability." (Trial Tr. (Felton), 997:13 – 998:4.)

373. Figure 18-4, relied upon by Actavis's experts, is a stylized representation of a hypothetical immediate release product and a typical sustained release product and does not represent an actual comparison of gabapentin immediate release and sustained release. (Trial Tr. (Mayersohn), 695:17 – 696:2, 720:21 – 721:6; Trial Tr. (Flanagan), 674:7-10; 16-21.)

374. If one were to assume that the immediate release product is Neurontin and the sustained release product is controlled-release gabapentin, one would not know whether gabapentin from the controlled-release product would be therapeutically effective or not. (Trial Tr. (Derendorf), 1036:5 – 1037:3.)

375. 21 CFR § 320 provides a goal and standards for approval and does not "tell you how to formulate." (Trial Tr. (Flanagan), 670:22 – 671:2.)

376. AB&P breaks 21 C.F.R. § 320 into seven elements, and also does not "tell you how to formulate" as Dr. Flanagan acknowledged. (Trial Tr. (Flanagan), 667:9 – 668:1, 670:22 – 671:2.)

377. Dr. Flanagan admitted that six of the seven requirements found in 21 C.F.R. § 320 articulated in the AB&P reference *are not found* in the WO '107 primary reference. (Trial Tr. (Flanagan), 669:1-4; DTX00323 (GRALISE_JDG_00000578).)

d. Neurontin Label Discloses Only IR Gabapentin Formulations Administered Three Times a Day

378. The Neurontin Label provides no information about controlled-release gabapentin formulation or the pharmacokinetics or therapeutic efficacy of gabapentin in a controlled-release dosage form. Instead, the label discusses immediate-release formulation of gabapentin. (Trial Tr. (Flanagan), 620:5-10.)

2. None of Actavis's Experts Has Expertise in Gabapentin Pharmacodynamics

379. It is undisputed that Dr. Flanagan is not an expert in gabapentin pharmacodynamics. (Trial Tr. (Flanagan), 679:1-4.)

380. It is also undisputed that Dr. Mayersohn is not an expert in gabapentin pharmacodynamics. (Trial Tr. (Mayersohn), 732:23-25.)

381. Dr. Gidal is an expert in gabapentin pharmacokinetics and pharmacodynamics, and he testified that one of skill in the art would not expect to have a therapeutically effective controlled-release gabapentin formulation. (Trial Tr. (Gidal), 842:8 – 846:15.)

3. Actavis Proffered Only Dr. Flanagan's Testimony To Show Obviousness of the '927, '989, and '756 Patent Claims Even Though Dr. Flanagan Acknowledged That He Is Not An Expert on Pharmacokinetics or Pharmacodynamics Which is Taught in Each and Every Asserted Gabapentin Patent Claim

382. Dr. Flanagan was qualified as an expert in pharmaceutical formulation, including the design and development of controlled-release dosage forms. (Trial Tr. (Flanagan), 552:10-13.)

383. It is undisputed that Dr. Flanagan is not an expert in pharmacokinetics. (Trial Tr. (Flanagan), 678:25 – 679:1.)

384. It is also undisputed that Dr. Flanagan is not an expert in pharmacodynamics of gabapentin. (Trial Tr. (Flanagan), 679:1-4.)

385. Yet only Dr. Flanagan provided expert testimony on whether the asserted claims of the '927, '989, and '756 Patents are rendered obvious. (Trial Tr. (Flanagan), 638:12-22; 639:7-10; Trial Tr. (Mayersohn), 719:20-720:4.)

386. By contrast, Dr. Derendorf, who is an expert on pharmacokinetics and pharmacodynamics, testified on the validity of all asserted gabapentin patent claims. (Trial Tr. (Derendorf), 1022:13-16.)

4. Actavis Expert Dr. Mayersohn Proffered No Opinion on the Obviousness of the '927, '989 and the '756 Patents and Proffered No Opinions on the motivation to Combine WO '107 With the Other References for Any of the Five Asserted Depomed Gabapentin Patents

387. Dr. Mayersohn testified that he was not opining at all with respect to the '927, '989 and '756 Patents and provided no opinion on motivation to combine references for any of the five Depomed asserted gabapentin patents. (Trial Tr. (Mayersohn), 719:20 – 720:1.)

5. The Differences Between the Identified Prior Art References and the Claimed Inventions

a. None of the References Teach a Controlled-release Gabapentin Dosage Form That the Asserted Gabapentin Patents Require

388. It is undisputed that the WO '107 reference does not mention gabapentin or a dosage form containing gabapentin. (Trial Tr. (Derendorf), 1021:9-12; Trial Tr. (Flanagan), 557:9-10.)

389. It is also undisputed that none of the remaining references identified by Actavis teach a controlled-release gabapentin dosage form. McLean discusses an immediate-release formulation. (Trial Tr. (Flanagan), 619:15-17.) The Neurontin label discusses immediate-release formulation of gabapentin. (Trial Tr. (Flanagan), 620:5-10.)

390. Each of the asserted Depomed Gabapentin Patent claims requires a controlled-release gabapentin dosage form. (JTX011-015.)

b. None of the References Teach Administration of a Therapeutically Effective Once Daily Controlled-release Gabapentin Dosage Form Recited in Claim 18 of the '927 Patent

391. It is undisputed that none of the Actavis asserted references disclose the once a day administration of a controlled-release gabapentin oral dosage form that claim 18 of the '927 Patent requires. ('927 Patent (JTX003); Trial Tr. (Flanagan), 557:9-10; 619:15-17; 620:5-10; (Felton), 982:14-22; 997:13 – 998:4.)

c. None of the References Teach Gabapentin From an Extended-release Dosage Form With Bioavailability That is at Least 80% as That From an Immediate Release Dosage Form

392. All asserted claims of the '989, '756, '332 and '992 Patents require bioavailability at least 80% as that from an immediate release form. Claim 10 of the '989 Patent, claims 1, 2, 5-7, 11 of the '756 Patent, claims 1, 6, 17, 22, 24 of the '332 Patent and claims 1, 5, 22 of the '992 Patent are asserted in this case.

393. It is undisputed that the WO '107 reference does not mention gabapentin. (Trial Tr. (Derendorf), 1021:9-12; Trial Tr. (Flanagan), 557:9-10.)

394. It is undisputed that the WO '107 reference does not specifically state or show data that its formulation achieved the goal of getting at least 80% bioavailability *in vivo* for *any* drug compared to an immediate release dosage form. (Trial Tr. (Derendorf), 1031:3-10; Trial Tr. (Flanagan), 576:8-13.)

395. Neither 21 CFR 320 nor AB&P teach this claim element. They are "general references. They do not discuss gabapentin" or teach "gabapentin or gabapentin bioavailability." (Trial Tr. (Felton), 997:13 – 998:4.)

396. It is undisputed that the WO '128 reference does not specifically state that its formulation would result in gabapentin with at least 80% bioavailability compared to that from an immediate release dosage form. (Trial Tr. (Derendorf), 1038:24 – 1039:3.)

d. None of the References Teach Gabapentin From an Extended-release Dosage Form With Lower C_{max} Than That From an Immediate Release Dosage Form

397. Asserted claims 1, 2, 5-7, 11 of the '756 Patent, 1, 6, 17 of the '332 Patent and 1, 5 of the '992 Patent require that the controlled-release gabapentin dosage form achieve *in vivo* a lower C_{max} than the immediate release gabapentin dosage form.

398. It is undisputed that the WO'107 reference does not specifically state that its formulation achieved lower C_{max} of a drug compared to that from an immediate release dosage form. (Trial Tr. (Derendorf), 1037:8-17; Trial Tr. (Flanagan), 614:19-21.)

e. None of the References Teach Gabapentin From an Extended-release Dosage Form With Longer T_{max} Than That From an Immediate Release Dosage Form

399. It is undisputed that the WO '107 reference does not mention gabapentin. (Trial Tr. (Derendorf), 1021:9-12; Trial Tr. (Flanagan), 557:9-10.)

400. It is undisputed that the WO '107 reference does not specifically state that its formulation achieved longer T_{max} of a drug compared to that from an immediate release dosage form. (Trial Tr. (Derendorf), 1038:1-8.)

401. AB&P also does not teach pharmacokinetic parameters from a gastric retained dosage form or from a gabapentin dosage form. Rather, AB&P "represents a conventional sustained-release drug delivery system" and is in fact "a schematic of a model compound." (Trial Tr. (Felton), 998:5-22.)

402. It is undisputed that the WO '128 reference does not specifically state that its formulation would result in gabapentin with longer T_{max} compared to that from an immediate release dosage form. (Trial Tr. (Derendorf), 1038:24 – 1039:3.)

f. None of the References Teach That Gabapentin Is Released "Over a Period of at Least Five Hours"

403. Asserted claims 18, 25, 26, 34, 61, 62 of the '927 Patent, claim 10 of the '989 Patent and claims 1, 2, 5-7, 11 of the '756 Patent require that the dosage form release gabapentin over a period of at least five hours *in vivo*. (JTX003-005.)

404. The dissolution curves depicted in the WO '107 reference are for metformin hydrochloride and metformin and gabapentin are not interchangeable drugs. (*See* FOF 460-481, *infra*.) Further, the dissolution curve is an *in vitro* dissolution graph that only focuses on the release of the drug in a test tube and no *in vivo* data is presented in the WO '107 reference showing that such a release is achieved in the dynamic environment of the stomach. (Trial Tr. (Felton), 994:1-19; 996-22 – 997:12.)

g. None of the References Teach That "At Least 40 Wt% of the Gabapentin Is Retained in the Dosage Form One Hour After Administration"

405. Asserted claims 18, 25, 26, 34, 61, 62 of the '927 Patent, claim 10 of the '989 Patent and claims 1, 2, 5-7, 11 of the '756 Patent require that "at least 40% wt% of the gabapentin is retained in the dosage form one hour after administration." (JTX003-005.)

406. It is undisputed that the WO '107 reference does not mention gabapentin. (Trial Tr. (Derendorf), 1021:9-12; Trial Tr. (Flanagan), 557:9-10.)

407. The WO '107 reference does not refer to gabapentin, and has no *in vivo* data to show that one hour after administration gabapentin is retained at least 40% wt after administration. (Trial Tr. (Felton), 994:21 – 995:10; 996-22 – 997:12.)

h. None of the References Teach That "The Gastric Retained Dosage Form Releases Gabapentin to the Stomach, Duodenum and Small Intestine" Recited by Claim 25 of the '927 Patent

408. Asserted claim 25 of the '927 Patent requires that the gabapentin controlled-release dosage form releases its drug to the stomach, duodenum and small intestine. (JTX003.)

409. It is undisputed that the WO '107 reference does not mention gabapentin. (Trial Tr. (Derendorf), 1021:9-12; Trial Tr. (Flanagan), 557:9-10.)

410. The WO '107 reference does not address gabapentin, does not have any *in vivo* data and further does not have any *in vitro* swelling data "to give one an idea" that it is even going to be gastrically retained. (Trial Tr. (Felton), 995:11 – 996:5.)

i. None of the References Teach "The Dosage Form Provides Administration of at Least 85 wt% of the Gabapentin to be Delivered Over a Period of About 5-12 Hours" Recited In Claim 26 of the '927 Patent

411. Claim 26 of the '927 Patent requires that the controlled-release gabapentin dosage from that 85% be delivered over a period of about 5-12 hours ('927 Patent (JTX003).)

412. It is undisputed that the WO '107 reference does not mention gabapentin. (Trial Tr. (Derendorf), 1021:9-12; Trial Tr. (Flanagan), 557:9-10.)

413. It is undisputed that there is no *in vivo* data presented in the WO '107 reference. (Trial Tr. (Felton), 996:6-21.)

6. No Motivation to Combine the WO '107 Reference With the Identified References to Produce the Inventions Recited in the Asserted Claims of the '927, '989, '756, '332 and '992 Patents

a. No Motivation to Combine Because no Disclosure in WO '107 That a Drug Would Be Absorbed Into the Blood Stream or be Therapeutically Effective as Required by Each of the Asserted Claims of the '927, '989, '756, '332 and '992 Patents

414. Each asserted claims of the gabapentin patents either expressly recites a pharmacokinetic parameter(s), such as AUC, Cmax or Tmax or it recites therapeutically effective gabapentin and sometime both. (JTX003, JTX004, JTX005, JTX006, JTX007.)

415. It is undisputed that the WO '107 reference does not disclose any pharmacokinetic element of gabapentin or any drug or any therapeutic administration of a drug. (Trial Tr. (Felton), 974:4-15; (Gidal), 842:7-17; (Flanagan), 656:1-3.)

416. It is undisputed that the WO '107 reference does not specifically state that its formulation achieved the goal of obtaining at least 80% bioavailability compared to an immediate release dosage form when delivered *in vivo* for any drug. (Trial Tr. (Derendorf), 1031:3-10.)

417. It is undisputed that the WO '107 reference does not specifically state that its formulation achieved the goal of obtaining lower Cmax compared to an immediate release dosage form when delivered *in vivo* for any drug. (Trial Tr. (Derendorf), 1037:3-10.)

418. It is also undisputed that the WO '107 reference does not specifically state that its formulation achieved the goal of obtaining longer T_{max} compared to an immediate release dosage form when delivered *in vivo* for any drug. (Trial Tr. (Derendorf), 1038:1-8.)

419. It is also undisputed that WO '107 reference does not have any data showing that the dosage form is gastrically retained. (Trial Tr. (Felton), 974:4-15; (Flanagan), 656:1-3, 656:6, 649:25 – 650:1.)

420. Without any information that the drug is in fact absorbed into the blood, there is insufficient information to know that gabapentin would in fact be absorbed into the blood stream with the appropriate kinetics such that its bioavailability will be at least 80% as that of an immediate release dosage form or with lower C_{max} or longer T_{max}. (Trial Tr. (Derendorf), 1031:17 – 1032:5; 1037:19-25; 1038:9-17.)

421. Accordingly, one of ordinary skill in the art would not be motivated to put gabapentin in the WO '107 dosage form in order to have gabapentin absorbed into the blood.

(1) WO '107 Teaches Vancomycin In Vitro, which One of Ordinary Skill Would Understand Would be a Poor Candidate for a Therapeutically Effective Dosage Form

422. Further, WO '107 provides *in vitro* dissolution curves for drugs like vancomycin which were known to be poorly absorbed orally and would be a poor candidate for therapeutically effective dosage form. (Trial Tr. (Felton), 1015:14-24; Trial Tr. (Derendorf), 1059:4-13.)

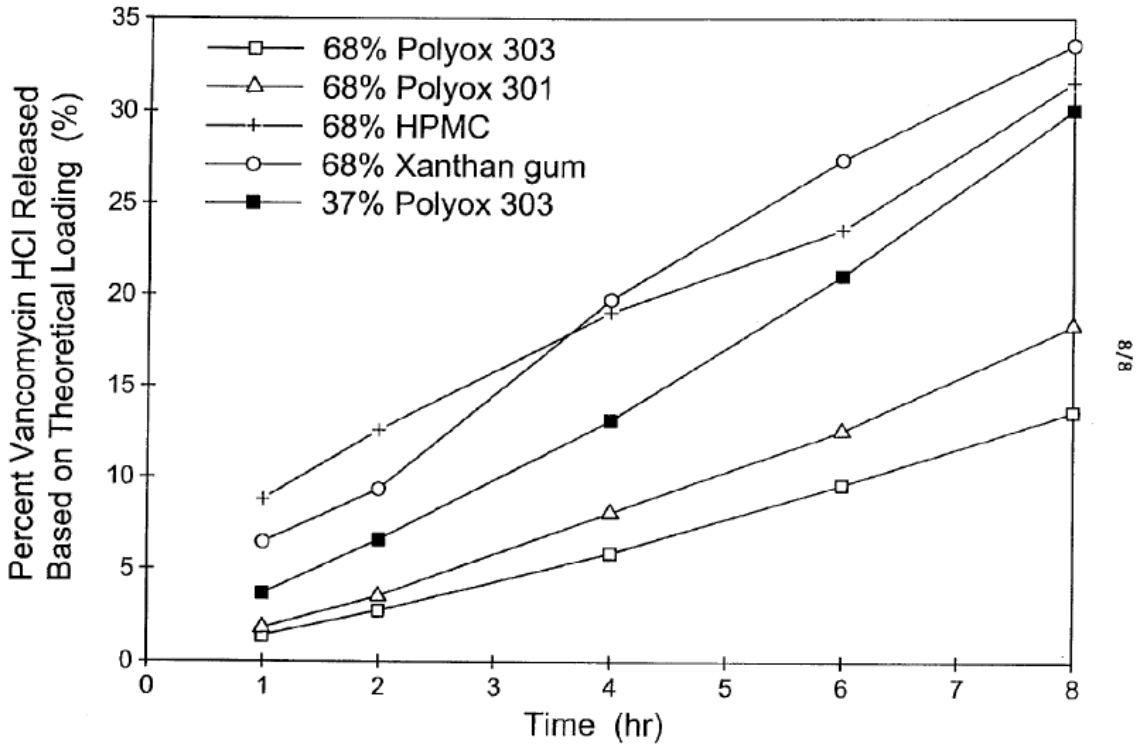


Fig. 8

(WO '107 (DTX00234), Fig. 8.)

423. Thus, one of skill in the art would understand that the WO '107 reference teaches a dosage form and not that the drug used in the WO '107 dosage form would necessarily be absorbed into the blood to result in certain

pharmacokinetic parameters or that the drug would be therapeutically effective. (Trial Tr. (Derendorf), 1059:17-23.)

b. A General Goal of at Least 80% AUC, Lower C_{max} and Higher Tmax of Gabapentin From a Controlled-Release Versus Immediate-Release Dosage Form is Insufficient Clear Motivation to Combine When None of the References Teach That Gabapentin From a Controlled-release Dosage Would Be Absorbed in Blood and Actavis Provided No Testimony From a Pharmacokinetics Expert on Motivation to Combine while Depomed Provided Testimony to the Contrary

424. Actavis's expert Dr. Flanagan testified that all controlled-release formulations are designed to meet the claim limitations of with loss in bioavailability (AUC) or lower C_{max}. (Trial Tr. (Flanagan), 608:14 – 609:10.) Dr. Flanagan further testified that without loss in AUC and lower C_{max} are the natural consequences of controlled-release dosages. (Trial Tr. (Flanagan), 609:14 – 610:1.)

425. Dr. Flanagan is not an expert in pharmacokinetics or pharmacodynamics. (Trial Tr. (Flanagan), 668:10-17, 678:25 – 679:4.)

426. Actavis's expert Dr. Mayersohn who is an expert on pharmacokinetics, provided no opinion on whether one of skill in the art would be motivated to combine any of the asserted references. (Trial Tr. (Mayersohn), 719:20-23.)

427. Depomed's expert Dr. Derendorf, an expert in pharmacokinetics (Trial Tr. (Derendorf), 1022:15-16) disagreed with Dr. Flanagan. Dr. Derendorf explained that controlled-release formulations can be of many types with different targets. Usually the relevant pharmacokinetic profile is one that would be therapeutically effective. Such a profile may have a lower C_{max}, but that is not always true. (Trial Tr. (Derendorf), 1032:21 – 1033:9.)

428. For example, the below figure from a textbook by Dr. Ansel compares pharmacokinetic profiles of two products. Formulation A is an immediate release product which shows rapid absorption and high C_{max}. Formulation B is an extended-release product with slower absorption and lower C_{max}. Both profiles have the same area under curve (AUC) so the total amount of drug delivered is the same. What is important in this figure is the line MEC, minimum effective concentration, and what it represents is the Pharmacokinetic (PK) / Pharmacodynamic (PD) relationship. If the concentration is above MEC, the drug is effective. (Trial Tr. (Derendorf), 1033:22 – 1034:21.)

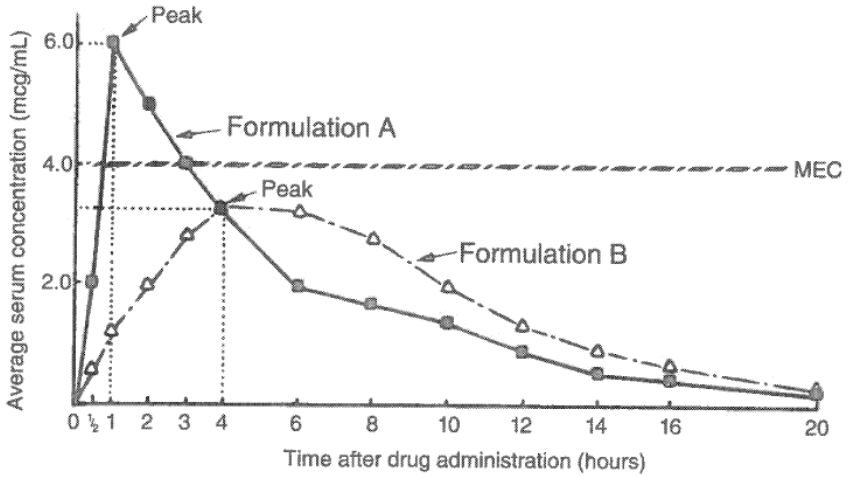


Fig. 4.6 *Serum concentration-time curve showing different peak height concentrations for equal amounts of drug from two different formulations following oral administration. (Courtesy of D.J. Chodos and A.R. DiSanto, The Upjohn Company.)*

429. In the above figure, the controlled-release product is below MEC. "So the fact that you slow down absorption to make a controlled-release product does not guarantee that you have an effective product." (Trial Tr. (Derendorf), 1034:22-25.)

430. Thus, a goal that AUC must be 80% as that of an immediate release dosage form, or that the C_{max} must be lower than that of an IR or that the T_{max} must be longer than that of an IR product is insufficient. If the controlled-release product is below MEC, the controlled-release product even though it meets all the PK goals, nonetheless would be therapeutically ineffective. Actavis does not rebut this. (Trial Tr. (Derendorf), 1034:22 – 1035:18.)

431. MEC for gabapentin is not known. Thus, simply by looking at a dose concentration profile, one would not know whether the drug is therapeutically effective or not. (Trial Tr. (Derendorf), 1035:5-18.)

(1) The FDA Noted the Effect of Food on Absorption and the Lack of a Known PK/PD Relationship for Gabapentin

432. The FDA uses these PK/PD relationships. If the company can show a validated PK/PD relationship, the FDA will waive clinical studies. In its absence, as in the case of gabapentin, the FDA expected the company to undertake a phase III clinical study. (Trial Tr. (Derendorf), 1035:19-25.)

433. The FDA noted the variable effect of food on gabapentin absorption and the surprising efficacy of Gralise, noting that the FDA would not have approved Gralise based only on pharmacokinetic and biopharmaceutic findings, without the benefit of clinical trial demonstrating efficacy. (Trial Tr. (Gidal), 839:13-25; 840:7-25.) It further noted that there was no data on the PK/PD relationship to treat PHN.

> It is certainly possible that the fluctuation in systemic exposure and the fat-dependent variability of absorption could affect the efficacy of G-ER [Gralise]. If the approval of G-ER rested solely on pharmacokinetic and biopharmaceutic findings, these issues could preclude approval. However, an adequate and well-controlled clinical trial was conducted in patients with PHN in which efficacy was demonstrated. . . . There is in fact no data regarding the pharmacokinetic/pharmacodynamic relationship of gabapentin for the treatment of PHN. Since G-ER did demonstrate efficacy in the clinical trial, where the fat content of the meals consumed with G-ER was not controlled, it appears that despite the fluctuations in systemic exposure and fat-dependent variability of absorption, G-ER was efficacious in the treatment of PHN in the clinical study population.

(Summary Review, Application Number: 022544Orig1s000, Center for Drug Evaluation and Research at 10, (PTX000265 (DEPOACT0816312)).)

434. Dr. Derendorf and Dr. Gidal confirmed that the PK/PD relationship for gabapentin was not known. (Trial Tr. (Derendorf), 1029:19-22; (Gidal), 842:7-17.)

435. Likewise, while it is reasonable to aim for a pharmacokinetic profile with at least 80% AUC and Cmax that is less than that of an immediate release dosage form and Tmax higher than that of an immediate release dosage form, (Trial Tr. (Derendorf), 1049:17 – 1050:8) that goal does not ensure that such a profile can be achieved. Given the variability in gabapentin absorption, one cannot clearly reasonably predict the pharmacokinetic profile that one would obtain based on *in vitro* dissolution data done for gabapentin.

c. No Specific Motivation Existed to Put Gabapentin in the WO '107 Dosage Form

436. One of ordinary skill in the art in October 2001 would not select gabapentin for use in the dosage form disclosed in WO '107 because:

a. Gabapentin is not mentioned in the WO '107 reference.

b. Gabapentin was known to be sensitive to degradation in acidic pH and the dosage form is designed to reside in the stomach for several hours;

c. The WO '107 reference "focuses quite a bit on a treatment for local effect in the stomach" and gabapentin is not used for such purpose;

d. "Gabapentin's absorption is influenced by the presence of food and the '107 patent application requires the drug product to be administered with food."

e. One of skill in the art would also not choose gabapentin based on the disclosure of metformin in the WO '107 reference—they are different chemicals. (*See* Section E.5.b below) For example, it is undisputed that Metformin is not sensitive to degradation in stomach PH. (Trial Tr. (Felton), 984:5-13; PTX000556 (DEPOACT0981923).) Further, absorption of metformin was not known to be affected by food as gabapentin was. Metformin is not transported by amino acid transporters.

f. One skilled in the art would not try to develop an extended-release dosage of gabapentin without knowing if release rate of the drug from the dosage form was appropriate. "Without understanding the saturable absorption kinetics, one of skill in the art would not know how quickly the drug needs to come out of that system or for that matter, what blood levels are necessary to achieve a therapeutic effect." (Trial Tr. (Felton), 987:16 – 989:2; 990:14-23; 991:4 – 992:24.)

437. Gabapentin was not identified in WO '107 reference as a potential drug to use in the '107 dosage form, even though Neurontin was a billion dollar a year drug. (Trial Tr. (Flanagan) 672:22-673:9.)

438. Further, the WO '107 reference states that the formulation is designed for gastric retention, but there is no evidence that the dosage forms "would be gastrically retained in vivo" for several hours. "There is no in vivo data that's presented, there is no swelling data that's presented and to be fair, at the time this was an emerging art and one of skill would look at these systems rather skeptically and would want to see some evidence that these systems are actually gastric retained." (Trial Tr. (Felton), 1012:6-23; Trial Tr. (Derendorf), 1024:10 – 1025:4.)

d. No Specific Motivation Existed to Select WO '107 Dosage Form Among the Large Number of Approaches That Were Available to Make a Gastric Retained Dosage Form

439. "The *Hwang* reference describes six different approaches that one of skill in the art in 1998 could have selected to achieve gastric retention." A swellable type system was just one of those approaches. (Trial Tr. (Felton), 968:22 – 969:8; *Hwang* DTX00222.)

(1) No Clear Teaching in the Art That a Particular Approach was Superior to Others

440. *Hwang* 1998 provides that "'there are good reviews on these devices,' indicating gastroretentive devices." But *Hwang* further provides that, "But most of the available references have too much data and many of them provide contradictory interpretations of the same approach." (Trial Tr. (Felton), 969:24 – 970:5)

441. *Davis* 2005 states: "Tablets formulated using hydrophilic polymers were tested in dogs and were found to have excellent gastroretentive properties (greater than 12 h) even in fasted state. Sadly, when the systems were tested in human volunteers using scintigraphy, the average time for emptying from the fasted stomach was just 33 minutes." (*Davis* PTX000274 (DEPOACT0970227).)

(2) The WO '812 Reference That Actavis Withdrew From Consideration in Fact Taught Away From Using a Matrix Based System Taught in the Asserted Patents Because It Taught a Matrix System Alone Would Not Survive the Dynamic Environment of the Stomach

442. Each of the asserted Depomed gabapentin claims requires a matrix or a single polymeric matrix for use in a gastric-retained dosage form. (JTX003-007.)

443. The WO '812 application, one of the prior art references identified by Actavis, teaches away from using the matrix system of the gabapentin patents. (DTX00229.)

444. Actavis's expert, Dr. Flanagan admitted that the WO '812 application was part of the art as of October 2001. (Trial Tr. (Flanagan) 652:24-653:1.)

445. The '812 application is a combination system, comprising at least two components, the matrix and a membrane, affixed or attached thereto. What this patent teaches is taken separately, neither of the matrix nor the membrane would retain in the stomach more than a conventional dosage form, but when the matrix is combined with the membrane, it achieves gastric retention. (Trial Tr. (Flanagan) 653:3-25; Trial Tr. (Felton) 980:18-981:6.)

446. WO '812 states:

> The basic concept underlying the delivery system of the present invention is the provision of a combination system, comprising at least two components, namely the matrix and the membrane affixed or attached thereto. *Taken separately, neither the matrix nor the*

> *membrane would retain in the stomach* ***more than a conventional dosage form***.

(DTX00229, p. 10, ll. 21-25 (Gralise_JDG_00002882) (emphasis added).)

447. This would tell one of skill in the art that "a matrix alone may not be sufficient to achieve gastric retention" and would teach away from the matrix system of the patents. (Trial Tr. (Felton), 979:20 – 981:10; DTX00229 (Gralise_JDG_00002882).)

7. No Reasonable Expectation of Success From Combining WO '107 With the Identified Prior Art References to Produce the Inventions Recited in the Asserted Claims of the '927, '989, '756, '332 and '992 Patents

a. No Reasonable Expectations of Success for All Asserted Gabapentin Claims

448. One of skill in the art would have no reasonable expectation of success of making the inventions recited in the asserted claims of the gabapentin patents ('927, '989, '756, '332 and '992 Patents) by combining the WO '107 reference with the references identified by Dr. Flanagan for several reasons.

a. *First*, gabapentin and metformin are not interchangeable; "they are distinct chemical entities and one can simply not substitute gabapentin in for metformin" in the WO '107 reference and expect therapeutically effective controlled-release gabapentin dosage form.

b. *Second*, "[g]abapentin is known to be sensitive to acidic environment of the stomach and so one would not want to put a drug that degrades in acid in the stomach where it's going to reside for a number of hours."

c. *Third*, gabapentin may not be made available in its narrow window of absorption. There is no *in vivo* data in the WO '107 reference showing that a dosage form would be in fact gastrically retained or that a gabapentin containing dosage form would be gastrically retained.

d. *Fourth*, gabapentin's release rate may not avoid saturation of absorption transporters.

e. *Fifth*, food affects gabapentin absorption.

f. *Finally*, there was a lack of known correlation between gabapentin plasma concentration and therapeutic effect. (Trial Tr. (Felton), 989:7 – 990:19; 990:25 – 992:24.)

b. No Reasonable Expectation of Success That Putting Gabapentin in WO '107 Dosage Form Would Result in a Therapeutically Effective Gabapentin as Recited in All Asserted Claims of the '927 Patent and Certain Claims of the '756, '332 and '992 Patents[3]

449. A person of ordinary skill in the art would not reasonably expect to achieve a therapeutically effective gabapentin by putting gabapentin in a WO '107 dosage form. (Trial Tr. (Derendorf), 1023:13-16.)

[3] The asserted claims from the '756, 332 and '992 Patents are, respectively, 1, 2, 5-7, 11; 1, 6, 17, 22, 24; and 1, 5, 22.

450. This is because the WO '107 reference does not provide any information about pharmacokinetics or any in vivo performance of any drug and further does not address gabapentin at all. One would need to do a study and measure the drug concentration in the blood and derive pharmacokinetic parameters before one can know whether it is reasonable to expect that gabapentin in the '107 dosage form would be therapeutically effective. (Trial Tr. (Derendorf), 1023:17 – 1024:3.)

(1) There Was No Known In Vitro / In Vivo Correlation (IVIVC) Between In Vitro Release of Gabapentin and In Vivo Absorption of Gabapentin and WO '107 and the Prior Art Fails to Teach This Correlation

451. Once the drug is absorbed, it produces a concentration profile that can be measured and characterized by pharmacokinetic parameters. (Trial Tr. (Derendorf), 1028:2-6.)

452. One of skill in the art can predict *in vivo* pharmacokinetics of a drug based on its in vitro dissolution if a relationship called "in vitro in vivo correlation ("IVIVC") *is known*. To determine the IVIVC, different dosage forms of a compound of interest are formulated and the *in vitro* dissolution rates on one hand and the *in vivo* pharmacokinetics on the other hand are experimentally determined. The data is analyzed to determine if there is correlation between the two pieces of information. This is known as an *in vivo in vitro* correlation or IVIVC. If the

correlation can be established in the form of a mathematical relationship, the correlation can then be used to make predictions of *in vivo* performance based on *in vitro* release studies. (Trial Tr. (Derendorf), 1028:18 – 1029:5.)

453. It is undisputed that such an IVIVC correlation *was not known* for gabapentin and that WO '107 does not teach this correlation. (Trial Tr. (Derendorf), 1029:6-7.)

454. In the absence of IVIVC correlation for gabapentin, one cannot reasonably predict pharmacokinetics of gabapentin based on the WO '107 reference, which does not even include *in vitro* dissolution studies of gabapentin. (Trial Tr. (Derendorf), 1029:23 – 1030:9.)

(2) There Was No Known Pharmacokinetic and Pharmacodynamics (PK/PD) Relationship of Gabapentin to Efficacy

455. Pharmacodynamics addresses the therapeutic effect of the drug as well as the undesired or side effects. One of skill in the art may ascertain through studies the relationship between the drug concentration in the body (PK) and the pharmacodynamics (PD) effect of the drug. This is called the PK-PD relationship. (Trial Tr. (Derendorf), 1029:8-18.)

456. The PK-PD relationship for gabapentin was unknown in 2001 and is unknown to this day. (Trial Tr. (Derendorf), 1029:19-22.) Actavis does not dispute this.

457. Thus, one cannot reasonably predict based on *in vitro* dissolution data of drugs such as metformin and captopril that one would achieve a therapeutically effective gabapentin by putting gabapentin in the WO '107 dosage form. (Trial Tr. (Derendorf), 1027:4-8; 1030:10-13.)

458. A person of ordinary skill in the art would also not reasonably expect to achieve a therapeutically effective gabapentin by putting gabapentin in a WO '107 dosage form given the variability in gabapentin absorption, including inter-person variability in absorption. (Trial Tr. (Gidal), 842:7 – 843:15.)

459. Further, without knowing pharmacokinetic data for gabapentin from a controlled-release formulation, which is not disclosed in the WO '107 reference, a person of ordinary skill in the art would not be able to reasonably predict therapeutic efficacy of gabapentin because of the variability in gabapentin absorption due to its narrow window of absorption, saturability of absorption, inter-person variability, food effect and dose effect, one would need to know something about the absorption characteristics of a product to predict whether or not it will be therapeutically effective. (Trial Tr. (Gidal), 843:21 – 844:12; 842:11-14.)

8. It Would Not Be Routine Experimentation To Put Gabapentin in the WO '107 Dosage Form to Achieve Success Because Metformin and Gabapentin Are Not Interchangeable and Their Differences Impact on the Dosage Forms Characteristics

a. One of Ordinary Skill would Understand That the Physicochemical Differences Between Metformin and Gabapentin Would Meaningfully Impact on the Release and Swelling Mechanisms of the Dosage Form and Thus No Clear Reasonable Expectation of Success

460. One of ordinary skill would have understood:

a. "[G]abapentin and metformin are different chemical entities and they're not interchangeable."

b. "Metformin is a cation, so it's positively charged, not only in the body at physiological pH, but also in the low pH of the stomach. Gabapentin is a zwitterion, it has a positive charge and a negative charge." (Trial Tr. (Felton), 982:23 – 983:8; 983:21 – 984:4.)

c. "Gabapentin degrades to a lactam and the rate at which it degrades is dependent on pH, moisture and excipients in the dosage form." "Metformin is actually stable at a low pH and does not form lactam." (Trial Tr. (Felton), 984:5-13.)

d. Metformin is more than twice as soluable as gabapentin at approximately 300 mg/ml for metformin versus 130 mg/ml for gabapentin. (Trial Tr. (Mayersohn), 730:5-14; *see also* (Hopfenberg), 953:8-10.) This difference is significant with respect to the potential development of a controlled-release form of gabapentin. (Trial Tr. (Felton), 984:25 – 985:9; 986:3-11.)

461. Actavis's expert Dr. Flanagan testified that drug solubility is one of the characteristics relevant for making controlled-release formulation and that high

solubility affected a drug's release differently than low solubility. (Trial Tr. (Flanagan), 561:14-25.)

462. Dr. Flanagan further acknowledged that gabapentin and metformin do not have the same solubility. (Trial Tr. (Flanagan), 562:4-6.)

463. These differences would impact the swelling, retention and release rates. Dr. Felton testified, "[T]he gastric retention mechanism, the swelling, is also related to the drug release and so adjusting the formulation to slow or increase the rate of the release could actually affect and probably would actually affect the swelling and, therefore, the gastric retention properties." "If you change the formulation to change the release rate, because the formulation swells and that's how it achieves gastric retention, by changing the composition of the tablet, the swelling behavior could change." (Trial Tr. (Felton), 984:14 – 985:9; 986:3-11.)

464. Dr. Hopfenberg explained that metformin and gabapentin would be released differently from a dosage form. Two factors drive diffusion: (a) solubility of the drug in the swollen matrix; (b) "diffusion coefficients" or diffusivity that provides how fast the drug can move through the dosage form. Gabapentin has a solubility more than two-fold less than that of metformin (135 mg/ml versus > 300 mg/ml) Diffusivity is related to the bulkiness of the molecule. Metformin is linear and rather small and would be more mobile than gabapentin which is a more bulky molecule with a ring structure that gives additional steric hindrance. Thus,

metformin would release at a much higher rate than gabapentin. (Trial Tr. (Hopfenberg), 951:21 – 952: 19.)

465. Thus, it would not be simply a matter of routine optimization to fine-tune gabapentin in the dosage form as compared to metformin. "[T]here would be a need to adjust the formulation so that the release of the gabapentin would be at some different rate and that release could affect the swelling, and therefore, the gastric retention." (Trial Tr. (Felton), 985:10-19, 986:3-11.)

b. The Different Pharmacokinetic Parameters Are Contrary to a Clear Expectation of Success Based on Routine Experimentation

466. It is further undisputed that the pharmacokinetic parameters for metformin and gabapentin would be different. (Trial Tr. (Derendorf), 1047:6-9.)

467. Dr. Derendorf testified that gabapentin and metformin differ from each other with respect to each of the pharmacokinetic properties: absorption, distribution and elimination, such that the exposure that would result from these two products would be quite different. (Trial Tr. (Derendorf), 1039:13-22.)

468. With respect to absorption of the drug, as of 2001, it was known that gabapentin is taken up by transporters. However, the mechanism of absorption of metformin was unclear.

469. Likewise, the Sambol reference (PTX000556) identifies two potential mechanism of absorption of metformin. (Trial Tr. (Derendorf), 1041:8 – 1042:9.)

> **One possible hypothesis for the dose-disproportionality in F is that because metformin is nonlipophilic and largely ionized in the gastrointestinal tract, its permeability is limited, perhaps increasingly as it transcends the tract**. Two observations were consistent with this hypothesis. First, the bioavailability of metformin is only approximately 30% to 60%, despite the absence of hepatic extraction and its high solubility, suggesting permeability limitations in its absorption. Second, the bioavailability of extended-release products was usually found to be less than that of the immediate-release product. **We cannot rule out, however, the possibility of a saturable active transport process**.

(PTX000556 (Sambol), p. 1018 (DEPOACT0981928).)

470. Dr. Derendorf testified that if metformin and gabapentin exhibit different absorption mechanisms, then he would not expect them to have similar pharmacokinetic behavior. This was not clearly understood in 2001. (Trial Tr. (Derendorf), 1042:10-15.)

471. It is also undisputed that the absorption window of gabapentin is not identical to that of metformin. (Trial Tr. (Derendorf), 1042:22 – 1043:11.)

472. Dr. Derendorf testified that even if the absorption window were the same, he would expect differences in absorption because the transporters would be different; they would have different affinity and therefore different efficiency in absorbing the drugs. (Trial Tr. (Derendorf), 1043:12:23.)

473. Dr. Derendorf explained that one would obtain different types of absorption profiles depending on the transporter in use. The profile would depend on the affinity of the transporter for the drug and the capacity of the transporter for

the drug—how much drug the transport can move into the blood stream. (Trial Tr. (Derendorf), 1044:6-20.)

474. In 2001, the affinity and capacity of L-type amino acid transporter for gabapentin was unknown and the metformin transport mechanism was unclear. (Trial Tr. (Derendorf), 1044:21 – 1045:2.)

475. Regarding the second pharmacokinetic property distribution, it is undisputed that distribution of gabapentin and metformin is different. Metformin has a 10-fold larger volume of distribution in tissues resulting in low plasma concentration, unlike gabapentin. (Trial Tr. (Derendorf), 1045:3-15.)

476. Dr. Derendorf explained that difference in distribution changes the pharmacokinetic profile obtained. For example, the Cmax value depends on the volume of distribution and the higher the volume of distribution, the lower the Cmax for the same amount of drug that enters the system. (Trial Tr. (Derendorf), 1046:16-25.)

477. Regarding the last pharmacokinetic property, elimination, Dr. Derendorf testified that although both metformin and gabapentin are eliminated by the kidneys, the mechanism of elimination is different. Whereas gabapentin is mainly eliminated by glomerular filtration, which does not involve transporters, metformin is eliminated by tuberous secretion, which involves transporters. Metformin is therefore eliminated at a much higher rate than gabapentin. Dr.

Derendorf concluded that one of skill cannot expect two drugs with different eliminations to have similar pharmacokinetics. (Trial Tr. (Derendorf), 1046:1-16.)

478. All of the foregoing grounds on pharmacokinetics are contrary to a clear reasonable expectation of success on combining WO '107 with gabapentin immediate release references.

9. Actavis Uses Hindsight Bias to Choose the WO '107 Reference After Knowing It Works

479. Until the disclosure in the '927 Patent application, a person of ordinary skill in the art would not have been motivated to select the WO '107 approach to address the problems with gabapentin nor had a clear reasonable expectation of success.

480. WO '107 is identified as a reference in the specification of the '927 Patent. ('927 Patent (JTX003), 5:50-62.)

481. The '927 Patent discloses that the WO '107 dosage form may be suitable for use in a gabapentin containing dosage form:

Dosage Form

> There are several drug delivery systems that are suitable for use in delivering gabapentin in the method of the invention as they are particularly tailored to be gastric-retained dosages, such as the swellable bilayer described by Franz, et al., U.S. Pat. No. 5,232,704; the multi-layer tablet with a band described by Wong, et al., U.S. Pat. No. 6,120,803; the membrane sac and gas generating agent described in Sinnreich, U.S. Pat. No. 4,996,058; the swellable, hydrophilic polymer system described in Shell, et al., U.S. Pat. No. 5,972,389 and

> Shell, et al., WO 9855107; all of which are incorporated herein by reference.

('927 Patent (JTX003), 5:50-62; Trial Tr. (Derendorf), 1052:24 – 1053:3.)

482. Dr. Flanagan admitted that until this litigation he was not aware of the WO '107 reference, despite his more than 35 years of experience. (Trial Tr. (Flanagan), 661:8-12.)

483. Dr. Flanagan further admitted that although the *Hwang* reference taught multiple approaches to gastric retention, he did not address any of those approaches. (Trial Tr. (Flanagan), 661:2-7.)

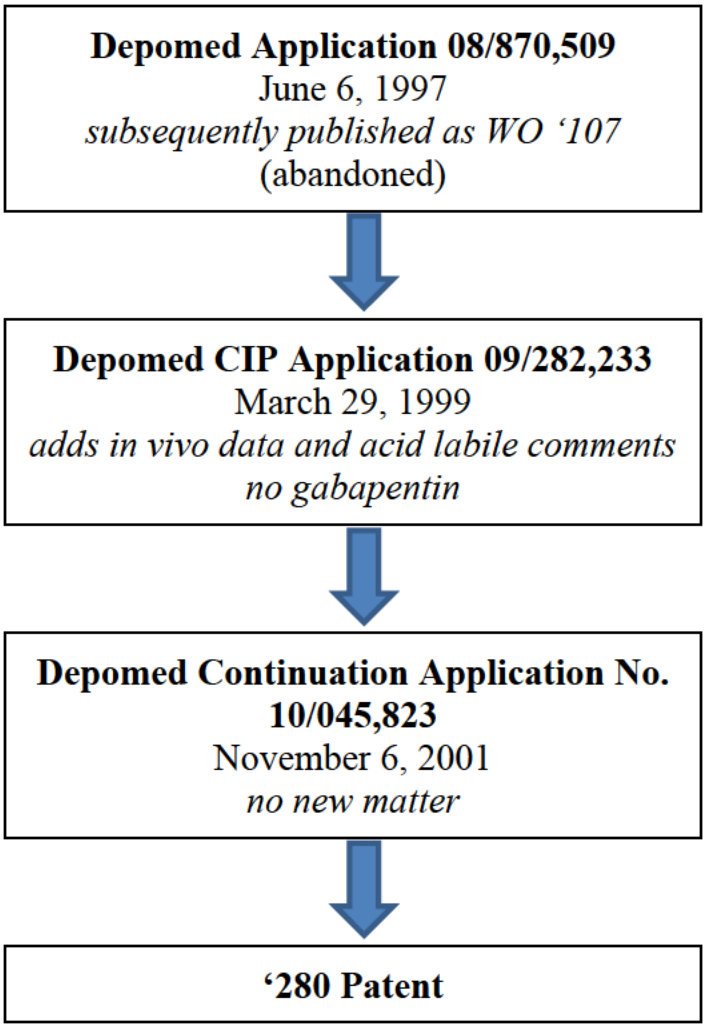
484. Given that the '927 Patent discloses that the WO '107 dosage form may be suitable for use in a gabapentin containing dosage form, it is hindsight bias to pick the WO '107 as a potential approach for gastric retention from the large number of available approaches, particularly when it is undisputed that WO '107 does not include in vivo data showing gastric retention. (Trial Tr. (Flanagan) 650:18-19.)

485. The June 6, 1997, U.S. equivalent of the WO '107 patent application that was published was ultimately abandoned. (DTX00234; JTX002 at "Related U.S. Application Data" ("application No. 08/870,509 . . . now abandoned"); *see also* Trial Tr. (Flanagan), 648:19 – 649:23; Trial Tr. (Derendorf), 1025:17-25.)

486. The prosecution histories show that on March 29, 1999, Depomed filed a continuation-in-part application (No. 09/282,233) to the original (and

abandoned) application that had published as WO '107. (JTX008.) This added significant new matter.

487. Depomed then filed a continuation of this application that issued as the '280 Patent. Thus,



488. Thus, the following in vivo disclosures showing gastric retention of the dosage forms reflected in the '280 Patent that were added in the 1999 Continuation-in-Part Application and are not in WO '107 are, *inter alia*, as follows:

EXAMPLE 9

This example illustrates the difference between subjects in the fed mode and subjects not in the fed mode in terms of the gastric retention of tablets of various sizes administered orally. Both Beagle dogs and human subjects were used.

Barium-containing tablets for oral administration were prepared from the following ingredients:

25% Barium Sulfate

30% PolyOx 303 (average molecular weight 7,000,000)

44.5% Hydroxypropylcellulose

0.5% Magnesium Stearate

For tests on Beagle dogs, 400-mg tablets measuring 5.8 mm diameterx5.1 mm heightx15.4 mm length were prepared in a tablet press at 2,500 psi pressure, and 800-mg tablets measuring 7.9 mm diameterx5.6 mm heightx19.1 mm length were prepared in a tablet press at 5,000 psi. Four beagle dogs were used, and the location of the tablets in the GI tract was followed using fluoroscopy. Two studies were initiated with the dogs. In the first study, each dog received two tablets (one 400-mg and one 800-mg) with a small amount of water after a 16-hour fast. In the second study, each dog received two tablets (one 400-mg and one 800-mg) thirty minutes after ingesting 50 grams of a standard meal. The location of the tablets (in or out of the stomach) was monitored every 30 minutes with the fluoroscope.

The fluoroscopy revealed that tablets that were administered while the dogs were in the fasted condition were emptied from the dogs' stomachs within 90 minutes: in two of the dogs, the stomachs contained no barium tablets at 30 minutes, in a third this was true at 60 minutes, and in the fourth at 90 minutes. Tablets that were administered while **the** dogs were in the fed state remained in the dogs' stomach for between 4 and 5 hours.

> Human tests were performed on ten normal adults of both sexes, each taking part in two trials, the first after fasting and the second after a bacon and egg breakfast of approximately 1,500 calories. The tablets used in the tests had the same composition as those used for the Beagle dogs and measured either 4 mmx4 mm or 6 mmx6 mm. The subjects were X-rayed at 30 minutes and at 1, 2, 4, 6, 8, 10, and approximately 12 hours after ingesting the tablets. In some subjects, visualization was achieved by ultrasound rather than X-rays.
>
> Imaging revealed that in the fasted trials, the tablets left the stomach in 30 minutes to one hour after administration. In the fed trials, the tablets demonstrated multiple-hour retention in the stomach in all subjects, 80% of the contents of all tablets being retained at 4 hours. Five of the ten subjects retained the tablets for 6 hours or more, and four of these five retained them for ten hours or more.

(JTX002, 16:37 – 17:23; Trial Tr. (Flanagan) 650:3-16.).) None of these data was in WO '107.

489. Depomed also performed additional research to determine whether acid labile drugs would be protected and added such subject matter in the 1999 Continuation-in-Part Application and are not in the WO '107 reference as follows:

> Another example is the class of drugs that are susceptible to degradation by exposure to gastric fluid, either by enzymes or low solution pH. The swellable hydrophilic matrix of the present invention protects the yet undelivered drug during the 4 to 6 hour delivery period during which the drug is continuously released while the dosage form is retained in the stomach. One example of such a drug is topiramate, a drug that is used for the treatment of epilepsy. Topiramate is absorbed preferentially high in the GI tract and is hydrolyzed by the acidic environment of the stomach. The dosage form and delivery system of the present invention will confine the delivery of the drug to the stomach and duodenum. As the drug diffuses out of the swollen matrix, it is susceptible to the acidic environment, but the undelivered drug is protected from degradation by the polymer matrix.

(JTX002, 3:1-15.) Thus, this shows that Depomed subsequently understood that acid labile drugs might be protected in the stomach.

490. The March 29, 1999, CIP does not mention gabapentin. (JTX002.)

491. Different Depomed inventors subsequently invented and filed in October 2001 provisional application directed to a gabapentin-containing gastric retained controlled-release dosage form and performed pharmacokinetic studies to confirm that gabapentin is absorbed into the bloodstream to be therapeutically effective. These inventions were first filed in the provisional priority application of October 25, 2001, for the separate family of Gabapentin Patents. All Gabapentin Patents arise out of a common application and specification. (JTX003-005; JTX007.)

492. There is no overlap between the inventors named on the face of the WO '107 (John W. Shell, Jenny Louie-Helm) and on the face of the Gabapentin Patents (Bret Berner, Sui Yuen Eddie Hou, Gloria Gusler). (*Compare* DTX00234 (WO '107), at p. 1, "Inventors/Applicants" *with, e.g.,* JTX003 ('927 Patent), at p. 1, "Inventors.")

493. That the '962 Patent names Bret Berner and Jenny Louie-Helm on its face does not in any way relate WO '107 with the Gabapentin Patents because the '962 Patent derives from a different parent application than either WO '107 or the Gabapentin Patents. (*Compare* JTX001 ('962 Patent), at p. 1, "Appl. No." *with*

DTX00234 (WO '107), at p. 1, "Priority Data" & "Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application" *with, e.g.*, JTX003 ('927 Patent), at p. 1, "Appl. No.".) The '962 Patent also covers wholly different inventions than those disclosed and claimed in WO '107 or the Gabapentin Patents.

494. The Gabapentin Patents set out the problem solved by their inventions as follows:

> **A once- or twice-daily dosage form of gabapentin would be expected to improve compliance** and therefore a controlled-release dosage form has some distinct advantages over the conventional immediate release formulations. In addition, a **controlled-release dosage form would lower the maximum plasma concentration**, and this may result in **reduced side effects**. Since gabapentin is absorbed high in the gastrointestinal tract, by means of a saturable transport mechanism, a gastric retained dosage form is particularly beneficial for delivery of gabapentin since **the dosage form would be able to keep the drug in the region of absorption and show improved bioavailability** by virtue of the slower release rate that avoids saturation of the carrier mediated transport of conventional dosages.

(*E.g.*, JTX003, 1:37-50 (emphasis added).)

495. The Gabapentin Patents describe their claimed inventions in terms that show the importance of pharmacokinetic measures to their operation:

DESCRIPTION OF THE INVENTION

> The invention relates to **a method of treating a disease state, such as epilepsy, by administering gabapentin in a once- or twice-daily gastric retained dosage form**. The gastric retained dosage form is particularly beneficial for delivery of gabapentin due to its prolonged transit in the upper gastrointestinal tract, which **allows the drug to be absorbed adequately in the preferred region of absorption**. In

> addition, a gastric retained dosage form **increases the t_{max}** and allows for a smoother, more prolonged anti-spasmolytic effect. This dosage form also **lowers the C_{max}** and may result in reduced incidence and/or severity of CNS side effects of the drug, such as somnolence, ataxia, fatigue and dizziness.

(*E.g.*, JTX003, 2:16-26 (emphasis added).)

496. Example 4 of the Gabapentin Patents demonstrates that its dosage forms achieve a beneficial pharmacokinetic profile upon administration to a patient in need of gabapentin treatment. No such data is in WO '107 for any drug, much less gabapentin. Indeed, the Gabapentin Patents disclose:

EXAMPLE 4

The pharmacokinetic profiles of the three formulations described in Example 3, administered as a 600-mg dose, were compared to Neurontin® immediate release 300-mg capsule in a randomized four-way cross-over experiment involving 15 healthy volunteers. Each subject was administered treatment of 600-mg gabapentin as one of the three GR™ formulations (1×600-mg tablet or 2×300-mg tablet) or Neurontin® capsules (2×300-mg) within 5 minutes of completing a high fat breakfast (FDA breakfast). Plasma samples were taken up to 48 hours post-dose. FIG. **2** illustrates the average plasma profile for the four treatments administered, and the pharmacokinetic data are summarized in tabulated form below.

Gabapentin Plasma Data - Average for 15 Subjects

Dosing		AUC_{inf} # ((ug/ml)*hr)	C_{max} # (ug/ml)	T_{max} (hours)
Neurontin ®, 300-mg	Mean:	46.65	4.72	3.93
2 × capsules	% CV:	19.0	20.2	15.1
GR6, 300-mg	Mean:	44.43	2.97	6.63
2 × tablets	% CV:	34.9	29.7	45.1
GR8, 300-mg	Mean:	41.84	3.10	5.63
2 × tablets	% CV:	34.4	26.2	34.9
GR8, 600-mg	Mean:	48.01	3.13	7.13
1 × tablet	% CV:	26.8	18.7	42.2

#Geometric Mean and Geometric % CV are reported here

As demonstrated in FIG. **2** and in tabulated form above, GR™ formulations demonstrate sustained release with a lower maximum plasma concentration and a larger value for the time of the maximum concentration compared to the immediate release capsules without loss in the bioavailability as measured by the plasma AUC_{inf}.

(*E.g.*, JTX003, 10:64 – 11:32 (Example 4) (highlighting added).)

497. The above *in vivo* data of gastric retention, pharmacokinetics and/or gabapentin were not taught in WO '107 reference, and as Depomed's experts testified, were necessary data and innovation before one of ordinary skill in the art would have a clearly reasonable expectation of success of combining gabapentin references with the WO '107 reference.

E. THE WO '128 PRIMARY REFERENCE TOGETHER WITH OTHER REFERENCES DOES NOT RENDER THE ASSERTED CLAIMS OF THE '332 AND '992 PATENTS OBVIOUS

1. WO '128 Is Only Identified as a Primary Reference Against the '332 and '992 Patent Claims and Does Not Disclose a Gabapentin Controlled-Release Dosage Form

498. Actavis's expert Dr. Flanagan testified that, for the asserted '332 and '992 patent claims, he relied on WO '128 in addition to WO '107 as the primary reference in rendering his obviousness opinion (Trial Tr. (Flanagan), 625:9-14.).

499. Actavis's expert Dr. Mayersohn testified only on the person of skill in the art's reasonable expectation of success if gabapentin were combined in the WO '128 dosage form in the context of the '332 and '992 Patent claims. He did not opine on motivation to combine these references. (Trial Tr. (Mayersohn), 719:20-23.)

500. "The WO '128 application is focused on gastroretentive delivery system of metformin hydrochloride." (Trial Tr. (Felton), 975:16-21.)

501. There is no mention of gabapentin in the WO '128 application. (Trial Tr. (Felton), 975:23-24.)

2. None of Actavis's Experts has Expertise in Gabapentin Pharmacodynamics

502. It is undisputed that Dr. Flanagan is not an expert in pharmacokinetics. (Trial Tr. (Flanagan), 678:25 – 679:1.)

503. It is undisputed that Dr. Flanagan is not an expert in gabapentin pharmacodynamics. (Trial Tr. (Flanagan), 679:1-4.)

504. It is also undisputed that Dr. Mayersohn is not an expert in gabapentin pharmacodynamics. (Trial Tr. (Mayersohn) 732:23-25.)

505. Dr. Gidal is an expert in gabapentin pharmacokinetics and pharmacodynamics. (Trial Tr. (Gidal), 828:6-13.)

3. Actavis relies Only on Dr. Flanagan's Testimony to Show Motivation to Combine Even Though Dr. Flanagan Acknowledged That He is not an Expert on Pharmacokinetics or Pharmacodynamics, Which is Taught in Each and Every Asserted Gabapentin Patent Claim

506. Only Dr. Flanagan provided expert testimony on behalf of Actavis on motivation to combine with respect to all asserted gabapentin patent claims. (Trial Tr. (Flanagan), 638:12 – 639:10; 639:7-10; Trial Tr. (Mayersohn) 719:20-720:4.)

507. By contrast, Dr. Derendorf, who is an expert on pharmacokinetics and pharmacodynamics, gave testimony applicable to the validity of all asserted

gabapentin patent claims. (Trial Tr. (Derendorf), 1022:13-24, 1030:14-23, 1032:6-15.)

4. The Differences Between the Identified Prior Art References and the Claimed Inventions

a. None of the References Teach a Controlled-release Gabapentin Dosage Form

508. It is undisputed that the WO '128 application does not disclose gabapentin or a dosage form containing gabapentin. (Trial Tr. (Felton), 975:16-24; (Derendorf), 1038:24-25.)

509. It is also undisputed that none of the remaining references identified by Actavis teaches a controlled-release gabapentin dosage form.

b. None of the References Teach Gabapentin From an Extended-Release Dosage Form With Bioavailability That is at Least 80% as That From an Immediate Release Dosage Form

510. It is undisputed that the WO '128 reference does not specifically state that its formulation would result in gabapentin with at least 80% bioavailability compared to that from an immediate release dosage form. (Trial Tr. (Derendorf), 1038:24 – 1039:3.)

511. Neither 21 CFR 320 nor AB&P teach this claim element. They are "general references. They do not discuss gabapentin" or teach "gabapentin or gabapentin bioavailability." (Trial Tr. (Felton), 997:13 – 998:4.)

c. None of the References Teach Gabapentin From an Extended-release Dosage Form With Lower C_{max} Than That From an Immediate Release Dosage Form

512. It is undisputed that the WO '128 reference does not specifically state that its formulation would result in gabapentin with lower C_{max} compared to that from an immediate release dosage form. (Trial Tr. (Derendorf), 1038:24 – 1039:22.)

d. None of the References Teach Gabapentin From an Extended-release Dosage Form With Longer T_{max} Than That From an Immediate Release Dosage Form

513. It is undisputed that the WO '128 reference does not specifically state that its formulation would result in gabapentin with longer T_{max} compared to that from an immediate release dosage form. (Trial Tr. (Derendorf), 1038:24 – 1039:22.)

514. AB&P also does not teach pharmacokinetic parameters from a gastric retained dosage form or from a gabapentin dosage form. Rather, AB&P "represents a conventional sustained-release drug delivery system" and is in fact "a schematic of a model compound." (Trial Tr. (Felton), 998:5-22.)

5. No Specific Motivation to Combine the WO '128 Reference With the Identified References To Produce The Inventions Recited in the Asserted Claims of the '332 and '992 Patents

515. One of ordinary skill in the art in October 2001 would not be motivated to combine the WO '128 reference with the references identified by Dr.

Flanagan to produce the inventions in the asserted claims of the '332 or '992 Patents. (Trial Tr. (Felton), 992:18 – 993:6.)

516. "The '128 application is focused on gastroretentive delivery system of Metformin hydrochloride." (Trial Tr. (Felton), 975:16-21.)

a. The WO '128 Application Provides a Four-Page Laundry List of Potential Drugs That Does Not Include Gabapentin as Suitable in the Dosage Form Despite Gabapentin Being a Billion Dollar Per Year Drug

517. The drug gabapentin is not mentioned in the WO '128 application even though the immediate release gabapentin, Neurontin, was a blockbuster drug and the WO '128 application provides four pages of drugs that may be employed. (Trial Tr. (Felton), 975:23 – 976:12; Trial Tr. (Flanagan) 672:22-673:11.) The four pages of drugs begin with "the following additional . . ." on page 23 of the '128 application (DTX00236). (Trial Tr. (Felton), 976:23 – 977:7.) An example from page 23 is shown:

The following additional type high water soluble drugs may be employed in the biphasic controlled release delivery system of the invention:

antihypertensives and antidepressants related to guanethidine (as disclosed in U.S. Patent No. 2,928,829) and related to guanoxyfen (as disclosed in BE612362);

antibiotics and viricides such as related to amidinomycin (as disclosed in JP 21,418);

stallimycin (as disclosed in DE 1,039,198);

Arphamenine B (as disclosed in published European Patent Application 85/133550A2);

chitinovorin-A (as disclosed in published European Patent Application 85/150,378A2 and U.S. Patent No., 4,723,004);

streptomycin (as disclosed in U.S. Patent No. 2,868,779);

SB-59 (as disclosed in Justus Liebigs, Ann. Chem. (1973) 7, 1112-1140);

TAN-1057-A (as disclosed in U.S. Patent No. 4,971,965);

streptoniazid (as disclosed in J. Am. Chem. Soc. (1953) 75, 2261);

immunostimulants related to

ST-789 (as disclosed in published European Patent Application 88/260588);

peptide hydrolase inhibitors related to

nafamastat (as disclosed in U.S. Patent No. 4,454,338);

gabexate (as disclosed in U.S. Patent No. 3,751,447);

sepimostat (as disclosed in U.S. Patent Nos. 4,777,182 and 4,820,730);

Factor Xa inhibitors related to

DX-9065a (as disclosed in published European Patent Application 92/0540051);

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(DTX00236 (WO ‘128) at GRALISE_JDG_00000079.)

518. The list continues onto page 25 and includes insulin among other drugs listed on line 34. The list continues to another page, page 26. (Trial Tr. (Felton), 978:3-9.)

0410833, EP 0422937 and EP 0422938; Ali et al, EP 0372486; Ohba et al, WO 90/02751 (PCT/JP89/00926); Klein et al, U.S. 4,952,562; Scarborough et al, WO 90/15620 (PCT/US90/03417); Ali et al, PCT/US90/06514 and PCT/US92/00999; the peptide-like compounds disclosed by Ali et al, EP 0381033 and EP 0384362; and the RGD peptide cyclo-N$^{\alpha}$-acetyl-Cys-Asn-Dtc-Amf-Gly-Asp-Cys-OH (in which Dtc is 4,4'-dimethylthiazolidine-5-carboxylic acid and Amf is 4-aminomethylphenylalanine).

The RGD peptide may be usefully included in the formulation of the invention in an amount up to about 600 mg/g of the hydrophilic phase or from 0.1 to 60 mg/g of the formulation.

Other peptides useful in the present invention include, but are not limited to, other RGD containing peptides such as those disclosed by Momany, U.S. 4,411,890 and U.S. 4,410,513; Bowers et al, U.S. 4,880,778, U.S. 4,880,777, U.S. 4,839,344; and WO 89/10933 (PCT/US89/01829); the peptide Ala-His-D-Nal-Ala-Trp-D-Phe-Lys-NH_2 (in which Nal represents β-naphthylalanine) and the peptides disclosed by Momany, U.S. 4,228,158, U.S. 4,228,157, U.S. 4,228,156, U.S. 4,228,155, U.S. 4,226,857, U.S. 4,224,316, U.S. 4,223,021, U.S. 4,223,020, U.S. 4,223,019 and U.S. 4,410,512.

Other suitable peptides include hexapeptides such as the growth hormone releasing peptide (GHRP) His-D-Trp-Ala-Trp-D-Phe-Lys-NH_2, (Momany, U.S. 4,411,890, the disclosure of which is herein incorporated by reference in its entirety). This may usefully be included in an amount up to about 250 mg/g of the hydrophilic phase or from 0.1 to 25 mg/kg of the formulation.

Suitable larger polypeptides and proteins for use in the controlled release formulations of the present invention include insulin, calcitonin, elcatonin, calcitoningene related peptide and porcine somatostatin as well as analogs and homologs thereof. Other suitable larger polypeptides include those disclosed by

519. Notably, despite being a billion dollar per year drug, the WO '128 application did not list gabapentin.

520. A person of ordinary skill in the art reviewing the four pages of drugs listed in the WO '128 application would not conclude that any or all of those drugs would be suitable for use in the dosage form described in the WO '128 application, but rather would be skeptical. There is no data about any of the listed drugs other than metformin. "Without any data, there is no evidence that any of these drugs would actually work. They're quite different in chemical structures." For example, one of the listed drugs is insulin and insulin is not absorbed orally. If one could develop a controlled-release version oral dosage form of insulin that "would be significantly more of a blockbuster than Neurontin IR in 1993." No such dosage form exists. (Trial Tr. (Felton), 978:11 – 979:19.)

b. Metformin and Gabapentin Are Not Interchangeable and the Limited PK Data on Metformin Is Insufficient to Motivate One of Skill in the Art to Combine WO '128 With the Gabapentin References

521. "[G]abapentin and metformin are different chemical entities and they're not interchangeable." (Trial Tr. (Felton), 983:2-8.)

522. "Metformin is a cation, so it's positively charged, not only in the body at physiological pH, but also in the low pH of the stomach. Gabapentin is a zwitterion, it has a positive charge and a negative charge." (Trial Tr. (Felton),

982:23 – 983:4.) Actavis's expert Dr. Mayersohn agreed that metformin and gabapentin differ in terms of charges. (Trial Tr. (Mayersohn), 716:5-7.)

523. "Gabapentin degrades to a lactam and the rate at which it degrades is dependent on pH, moisture and excipients in the dosage form." "Metformin is actually stable at a low pH and does not form lactam." (Trial Tr. (Felton), 984:5-13; *see* PTX000549 at DEPOACT0981788.)

524. It is undisputed that gabapentin and metformin do not have the same solubility. (Trial Tr. (Flanagan), 562:4-6; (Mayersohn), 705:19-20.) Metformin is more than twice as soluable as gabapentin at approximately 300 mg/ml for metformin versus 130 mg/ml for gabapentin. (Trial Tr. (Mayersohn), 730:5-14; (Hopfenberg), 951:21 – 953:19.)

525. Actavis's expert Dr. Flanagan testified that drug solubility is one of the characteristics relevant for making controlled-release formulation and that high solubility affects a drug's release differently than low solubility. (Trial Tr. (Flanagan), 561:14-25.)

526. Actavis's expert Dr. Mayersohn acknowledged that as he was not a formulator, he could not offer definitive answer to how solubility might impact the dosage form. (Trial Tr. (Mayersohn), 730:15-19.)

527. Depomed's expert Dr. Felton, who is a formulator, explained that the difference in the solubility of metformin versus gabapentin is significant with

respect to the potential development of a controlled-release gabapentin formulation. "[T]he gastric retention mechanism, the swelling, is also related to the drug release and so adjusting the formulation to slow or increase the rate of the release could actually affect and probably would actually affect the swelling and, therefore, the gastric retention properties." "[I]f you change the formulation to change the release rate, because the formulation swells and that's how it achieves gastric retention, by changing the composition of the tablet, the swelling behavior could change." (Trial Tr. (Felton), 984:14 – 985:9; 986:3-11.)

528. Metformin and gabapentin would be released differently from a dosage form. Two factors drive diffusion: (a) solubility of the drug in the swollen matrix; (b) "diffusion coefficients" or diffusivity that provides how fast the drug can move through the dosage form. Gabapentin has a solubility more than two-fold less than that of metformin (135 mg/ml versus > 300 mg/ml) Diffusivity is related to the bulkiness of the molecule. Metformin is linear and rather small and would be more mobile than gabapentin which is a more bulky molecule with a ring structure that gives additional steric hindrance. Thus, metformin would release at a much higher rate than gabapentin. (Hopfenberg testimony; 951:21 – 953:19.)

529. Thus, it would not be simply a matter of routine optimization to fine-tune gabapentin in the dosage form as compared to metformin. "[T]here would be a need to adjust the formulation so that the release of the gabapentin would be at

some different rate and that release could affect the swelling, and therefore, the gastric retention." (Trial Tr. (Felton), 985:10-19, 986:3-11.)

530. Further, the extent of gastric retention with the WO '128 dosage form when compared to the '927 dosage form appears to be different. For example, only a modest increase in T_{max} is seen with metformin in the WO '128 dosage form (from 3.5 hours to 5 hours), as opposed to the much larger increase in T_{max} with gabapentin in the '927 dosage form (from 4 to 7 hours with Neurontin and 9.5 hours with Actavis product). (DTX00236 (GRALISE_JDG_00000090); JTX003 (DEPOACT0976795).)

531. It is further undisputed that the pharmacokinetic numbers for metformin and gabapentin would be different. (Trial Tr. (Derendorf), 1047:6-9; (Mayersohn), 718:12-15.)

532. Dr. Derendorf testified that gabapentin and metformin differ from each other with respect to each of the pharmacokinetic properties: absorption, distribution and elimination, such that the exposure that would result from these two products would be quite different. (Trial Tr. (Derendorf), 1039:13-22.)

533. With respect to absorption of the drug, as of 2001, it was known that gabapentin is taken up by transporters. However, the mechanism of absorption of metformin was unclear. For example, the WO '128 reference provides two theories for low bioavailability of metformin: (a) saturable transport process; and

(b) permeability transit time limited absorption. (Trial Tr. (Derendorf), 1039:23 – 1040:17.)

> Its oral bioavailability is in the range of 40 to 60% decreasing with increasing dosage which suggests some kind of saturable absorption process, or permeability/transit time limited absorption.

(DTX00236 at 1:22-26.)

534. Likewise, the Sambol reference (PTX000556) identifies the same two potential mechanism of absorption of metformin. (Trial Tr. (Derendorf), 1041:8 – 1042:9.)

> **One possible hypothesis for the dose-disproportionality in F is that because metformin is nonlipophilic and largely ionized in the gastrointestinal tract, its permeability is limited, perhaps increasingly as it transcends the tract**. Two observations were consistent with this hypothesis. First, the bioavailability of metformin is only approximately 30% to 60%, despite the absence of hepatic extraction and its high solubility, suggesting permeability limitations in its absorption. Second, the bioavailability of extended-release products was usually found to be less than that of the immediate-release product. **We cannot rule out, however, the possibility of a saturable active transport process**.

(PTX000556 (Sambol), p. 1018 (DEPOACT0981928).)

535. Dr. Derendorf explained that the saturable transport process implies that saturable transporters are involved. As for the permeability transit time limited absorption, Dr. Derendorf explained that metformin is a very highly water soluble compound and such compounds do not cross cell membranes easily and therefore have poor permeability. For drugs with poor permeability, exposure to

membrane becomes a factor, so the transit time that the drug travels down the absorption site becomes important. (Trial Tr. (Derendorf), 1040:18 – 1041:7.)

536. Dr. Derendorf testified that if two drugs exhibit different absorption mechanisms, then he would not expect them to have similar pharmacokinetic behavior. (Trial Tr. (Derendorf), 1042:10-15.)

537. It is also undisputed that the absorption window of gabapentin is not identical to that of metformin. (Trial Tr. (Derendorf), 1042:22 – 1043:11; (Mayersohn), 715:9-11.)

538. Dr. Derendorf testified that even if the absorption window were the same, he would expect differences in absorption because the transporters would be different; they would have different affinity and therefore different efficiency in absorbing the drugs. (Trial Tr. (Derendorf), 1043:12:23.)

539. Dr. Derendorf explained that one would get different types of absorption profiles depending on the transporter in use. The profile would depend on the affinity of the transporter for the drug and the capacity of the transporter for the drug—how much drug the transport can move into the blood stream. (Trial Tr. (Derendorf), 1044:6-20.)

540. Actavis's expert Dr. Mayersohn agreed that metformin and gabapentin use different transporters. (Trial Tr. (Mayersohn), 728:4-6.)

541. Dr. Mayersohn further acknowledged that the rate at which the two transporters operate was probably unknown in 2001. (Trial Tr. (Mayersohn), 728:10-12; 734:14-25.)

542. In 2001, the affinity and capacity of L-type amino acid transporter for gabapentin was unknown and metformin transport mechanism was unclear. (Trial Tr. (Derendorf), 1044:21 – 1045:2.)

543. Regarding the second pharmacokinetic property distribution, it is undisputed that distribution of gabapentin and metformin is different. (Trial Tr. (Mayersohn), 716:21-25. Metformin has a 10-fold larger volume of distribution in tissues resulting in low plasma concentration, unlike gabapentin. (Trial Tr. (Derendorf), 1045:3-15.)

544. Dr. Derendorf explained that difference in distribution changes the pharmacokinetic profile obtained. For example, the Cmax value depends on the volume of distribution and the higher the volume of distribution, the lower the Cmax for the same amount of drug that enters the system. (Trial Tr. (Derendorf), 1046:16-25.)

545. Regarding the last pharmacokinetic property, elimination, Dr. Derendorf testified that although both metformin and gabapentin are eliminated by the kidneys, the mechanism of elimination is different. Whereas gabapentin is mainly eliminated by glomerular filtration, which does not involve transporters,

metformin is eliminated by tuberous secretion, which involves transporters. Metformin is therefore eliminated at a much higher rate than gabapentin. Dr. Derendorf concluded that one cannot expect two drugs with different eliminations to have similar pharmacokinetics. (Trial Tr. (Derendorf), 1046:1-16; DTX00267 (GRALISE_JDG_00000129); PTX000556 (DEPOACT0981923).)

546. Actavis's expert Dr. Mayersohn agreed that the numeric clearance values for metformin and gabapentin are different. (Trial Tr. (Mayersohn), 734:2-8.)

547. Dr. Mayersohn further agreed that ADME (absorption, distribution, metabolism, elimination) are the four elements of pharmacokinetics. (Trial Tr. (Mayersohn), 734:19-22.)

548. Dr. Mayersohn agreed that the outcome of ADME, and not just absorption, at any moment in time is the concentration of drug in the plasma. (Trial Tr. (Mayersohn), 733:1-3.)

549. Finally, Dr. Derendorf compared the pharmacokinetic parameters of IR and extended-release metformin from the WO '128 reference with the pharmacokinetic parameters of IR and extended-release gabapentin from the '927 Patent. Dr. Derendorf noted the differences in the pharmacokinetic parameters in the two drugs, in particular the modest increase in T_{max} with metformin (from 3.5 hours to 5 hours), and the much larger increase in T_{max} with gabapentin (from 4 to

7 hours with Neurontin and 9.5 hours with Actavis product). Dr. Derendorf concluded that the two drugs in the different dosage forms behave differently in the way they affect Tmax and one of ordinary skill in the art would not reasonably expect gabapentin in the WO '128 dosage form to behave similarly as metformin. (Trial Tr. (Derendorf), 1046:16 – 1048:9.)

550. "There is also the issue of the saturable absorption transporter system and metformin and gabapentin are using different absorption transporters and so the in vivo data for metformin really is not applicable to gabapentin." (Trial Tr. (Felton), 985:20-23.)

551. Further, gabapentin is a "different compound with different properties and different solubilities, different therapeutic efficacies, different necessary blood levels and absorb through a different transporter system." (Trial Tr. (Felton), 985:23 – 986:2.)

552. Actavis's expert Dr. Mayersohn agreed that if absorption of drug were to slow appreciably, such as when the dosage form is past the window of absorption, the AUC curve would decline and if the absorption declines at fastest speed, the AUC curve would be parallel to AUC curve of the immediate release. (Trial Tr. (Mayersohn), 722:22 – 723:2; 723:8-9; 724:2-4.)

553. Thus, different drugs may exhibit different AUC curves depending on the extent of gastric retention and the site of absorption of drug, among other

factors. The *in vivo* data for metformin would not be applicable to gabapentin. (Trial Tr. (Felton), 985:23 – 986:2.)

554. All of the foregoing physicochemical and pharmacokinetic differences are contrary to Actavis's assertion of a clear motivation to combine WO '128 with the gabapentin IR references to produce the claimed and asserted '332 and '992 inventions.

c. Gabapentin is not a Suitable Candidate to put in a Dosage Form That is Dependent on Food and is Exposed to Stomach Environment for an Extended Period of Time

555. Gabapentin would not be a suitable candidate for the WO '128 dosage form because (a) gabapentin degrades to lactam at a quicker rate in the acidic environment of stomach; and (b) the food effect of gabapentin. (Trial Tr. (Felton), 976:14-20.)

6. No Reasonable Expectation of Success From Combining the WO '128 Reference With the Identified References to Produce the Inventions Recited in the Asserted Claims of the '332 and '992 Patents

556. One of ordinary skill in the art in October 2001 would have no reasonable expectation of success by combining the WO '128 reference with the references identified by Dr. Flanagan to produce the inventions in the asserted claims of the '332 or '992 Patents. (Trial Tr. (Felton), 992:25 – 993:6.)

557. All asserted claims of the ’332 and ‘992 Patents recite gabapentin from an extended-release dosage form with bioavailability that is at least 80% of that from an immediate release dosage form. Further, some of the asserted claims recite gabapentin with lower C_{max} while other asserted claims recite gabapentin with longer T_{max} compared to that from an immediate release dosage form. (JTX006; JTX007.)

558. In addition, claims 17 and 24 of the ‘332 Patent and claim 22 of the ‘992 Patent recite therapeutic efficacy of gabapentin. (JTX006; JTX007.)

559. It is undisputed that the ‘128 reference does not mention gabapentin or include gabapentin pharmacokinetic data or therapeutic efficacy. (Trial Tr. (Derendorf), 1038:24 – 1039:3; Trial Tr. (Gidal), 844:13-24 (Mayersohn), 726:1-6; 736:7-10.)

560. A person of ordinary skill in the art would also not reasonably expect to achieve a therapeutically effective gabapentin by putting gabapentin in a WO ‘128 dosage form because the WO ‘128 dosage form provides no information about gabapentin, but instead provides data about a completely different drug metformin. One cannot translate the pharmacokinetic data provided for metformin in WO ‘128 and reasonably predict similar result with gabapentin. Metformin and gabapentin are entirely different chemical molecule with different absorption mechanisms, which is important. As Actavis’s expert Dr. Mayersohn testified,

absorption is complicated. It is very simple to say that they're both absorbed in the upper small intestine, but they involve different transporters and different mechanisms. One of skill in the art would not translate metformin pharmacokinetic data to expect the same for gabapentin and ignore all the differences and say it does not matter. (Trial Tr. (Gidal), 844:25 – 846:15.)

561. Further, without knowing pharmacokinetic data for gabapentin from a controlled-release formulation, which is not disclosed in the WO '107 reference, a person of ordinary skill in the art would not be able to reasonably predict therapeutic efficacy of gabapentin because of the variability in gabapentin absorption due to its narrow window of absorption, saturability of absorption, inter-person variability, food effect and dose effect, one would need to know something about the absorption characteristics of a product to predict whether or not it will be therapeutically effective. (Trial Tr. (Gidal), 843:21 – 844:12; 842:11-14.)

VII. PROPOSED FINDINGS OF FACT – OBJECTIVE EVIDENCE OF NONOBVIOUSNESS ON THE GABAPENTIN PATENTS

A. GRALISE® IS AN EMBODIMENT OF THE ASSERTED GABAPENTIN PATENT CLAIMS

562. Defendants have stipulated that Gralise embodies the asserted claims of the '927, '989, '756, '332 and '992 Patents. (ECF No. 328 at 29 [Stip. Facts], ¶¶ 112-16).

B. GRALISE® SATISFIED AN UNMET NEED THAT EXISTED SINCE 1994 FOR AN EFFECTIVE EXTENDED RELEASE GABAPENTIN DOSAGE FORM

563. It is undisputed that Neurontin, an immediate release dosage form of gabapentin was approved by the FDA in 1993 and marketed by Warner-Lambert and Pfizer. (Trial Tr. (Flanagan), 679:5-7.)

564. It is also undisputed that the first sustained release gastric retained oral dosage form for gabapentin was Gralise, which was approved in 2011. (Trial Tr. (Flanagan), 679:8-11.)

1. The Parties' Experts and Their Testimony

565. The Court qualified as an expert witness each party's pain management physician: Dr. Brown for Depomed (Trial Tr. (Brown), 869:17-20) and Dr. Sinatra for Actavis. (Trial Tr. (Sinatra), 895:21-24.)

566. Depomed's expert, Dr. Michelle Brown, testified that a long-felt need existed for a controlled release formulation of gabapentin as described in the patented claims as of October 2001 and that Gralise, the stipulated embodiment of the asserted claims of the Gabapentin Patents, met that need. (Trial Tr. (Brown), 870:1-7.)

567. In rendering her opinion, Dr. Brown considered resources pain management physicians would use in their clinical practices to determine how best

to treat neuropathic pain, including journal articles, clinical studies, and drug package inserts. (Trial Tr. (Brown), 868:23-869:3.)

568. Dr. Brown also relied on her clinical experience, which includes her continuous treatment of neuropathic pain for twenty-two years, during which time she has prescribed numerous drugs, among them both immediate release and controlled release formulations of gabapentin. (Trial Tr. (Brown), 867:18–868:19.)

569. Dr. Brown also serves on the Depomed Speaker's Bureau for Gralise, and in that capacity Dr. Brown discusses with other doctors their prescribing practices with respect to the controlled release formulation of gabapentin of the asserted claims. (Trial Tr. (Brown), 884:12–885:1.)

570. Dr. Brown is not a POSA under either party's definition, but Dr. Brown did not offer an opinion from the perspective of a POSA. (Trial Tr. (Brown), 869:7-16.)

571. Defendants' expert, Dr. Raymond Sinatra, failed to provide the contrary opinion that in October 2001 there did not exist a long-felt need for a controlled release formulation of gabapentin as described in the asserted claims of the Gabapentin Patents. (Trial Tr. (Sinatra), 895:13-23.)

572. Dr. Sinatra instead limited his testimony to his personal prescribing practices, a review of the uses of Gralise (with which he has no personal experience) and immediate release formulations of gabapentin, and other

medications that can be used to treat neuropathic pain. (Trial Tr. (Sinatra), 895:13-23, 897:14–898:4, 904:13-22, 905:7-14, 907:16-20.)

573. Dr. Sinatra did not testify that he is a POSA under either party's definition.

574. Although Dr. Sinatra has prescribed gabapentin immediate release formulations to treat neuropathic pain since 1996, Dr. Sinatra has no personal experience with controlled release gabapentin, has never prescribed controlled release gabapentin, and did not speak to any doctors who have prescribed controlled release gabapentin in connection with forming his opinions in this case. (Trial Tr. (Sinatra), 897:14–898:4, 904:13-22, 905:7-14.)

2. Dr. Brown's Unrebutted Opinion of Existence of Long-Felt Need

575. As of October 2001, the only formulation of gabapentin on the market was an immediate release formulation, brand name Neurontin. (Trial Tr. (Brown), 870:14–871:19.)

576. The FDA approved Neurontin in December 1993, and Parke-Davis launched it in February 1994. ECF No. 328 at 30 [Stip. Facts], ¶¶ 119-120.

577. Neurontin has two drawbacks that contributed to the long-felt need in October 2001 for a controlled release gabapentin formulation as taught by the asserted claims of the Gabapentin Patents: the need for it to be dosed three times a

day and the fact that it has an unfavorable side effect profile when administered at a dosage necessary to manage neuropathic pain. (Trial Tr. (Brown), 871:6-15.)

578. The requirement of thrice daily dosing of Neurontin is a drawback because patients prefer to take fewer doses of a drug, and, as a result, doctors observe better patient compliance with drugs required to be taken only once daily as compared to drugs that must be taken multiple times a day. (Trial Tr. (Brown), at 871:16–872:2.)

579. Dr. Gidal, another of Depomed's invalidity experts, also testified that patients often forget to take a dose of Neurontin and that patients view as inconvenient the thrice daily dosing schedule for Neurontin. (Trial Tr. (Gidal), 818:2-819:14.)

580. A patient suffering from neuropathic pain who fails to comply with the thrice daily dosing of the recommended dosages of immediate release gabapentin will experience lower efficacy and more pain as compared to a patient who takes all three daily doses of immediate release gabapentin at the recommended dosages. (Trial Tr. (Brown), 872:3-7, 877:9-21.)

581. It is undisputed that patients have failed to comply with the three-times-a-day dosing schedule of the recommended dosages of immediate release gabapentin, as both Dr. Brown and Dr. Sinatra testified that they have had patients

skip doses of Neurontin. (Trial Tr. (Brown), 872:8–873:14, (Sinatra), 902:17–903:4.)

582. Dizziness and somnolence are the most common side effects of Neurontin when taken to treat neuropathic pain. (Trial Tr. (Brown), 873:16–874:13, 875:17–876:24; PTX000196 (DEPOACT0026320); PTX000266 (DEPOACT0872487-88) (peer reviewed literature containing discussion of side effects of immediate release gabapentin).)

583. The side effects of somnolence and dizziness limit the effectiveness of Neurontin to treat neuropathic pain because patients may elect to skip a dose in order to avoid feeling somnolent or dizzy. (Trial Tr. (Brown), 874:18–875:1, 877:9-15.)

584. Pain management physicians started prescribing Neurontin to treat neuropathic pain in 1994. (Trial Tr. (Brown), 868:12-14.)

585. Pain management physicians recognized fairly quickly after the introduction of Neurontin in the market in 1994 – and before October 2001 – that the side effects of somnolence and dizziness limited the effectiveness of Neurontin to treat neuropathic pain. (Trial Tr. (Brown), 868:12-14, 877:2-9; *see also* Trial Tr. (Gidal), 818:2-819:14 (testifying a need existed for once daily dosage form of gabapentin soon after Neurontin became available).) ECF No. 328 at 30 [Stip. Facts], ¶¶ 119-120.

586. It is undisputed that patients skip doses of immediate release gabapentin due to its side effects, as both Dr. Brown and Dr. Sinatra testified that they have had patients skip doses of immediate release gabapentin. (Trial Tr. (Brown), 882:5-13, (Sinatra) 902:17-903:4.)

587. Up to fifty percent of the patients suffering from neuropathic pain Dr. Brown has treated with Neurontin or immediate release gabapentin have had to discontinue use because of the side effects of somnolence and/or dizziness. (Trial Tr. (Brown), 882:5-13.)

588. Likewise, Dr. Sinatra has had patients skip doses of immediate release gabapentin due to its side effects. (Trial Tr. (Sinatra), 902:17-903:4.)

3. Gralise Which Embodies the Claims of the Asserted Patents Met the Long-Felt Need

589. Gralise met the long-felt need for a controlled release formulation of gabapentin. (Trial Tr. (Brown), 870:8-9.)

590. Because the parties stipulated that Gralise embodies the asserted claims of the Gabapentin Patents, the fact that Gralise met the long-felt need means the asserted claims of the Gabapentin Patents meet that long-felt need. ECF No. 328 at 29 [Stip. Facts], ¶¶ 111-116. (*See also* Trial Tr. (Brown), 870:10-13.)

591. The parties stipulated that Gralise became available in October 2011 and is the first and only controlled release gabapentin formulation on the market.

ECF No. 328 at 28 [Stip. Facts], ¶¶ 107, 108. (*See also* Trial Tr. (Brown), 878:4-5.)

592. Gralise is as effective as immediate release gabapentin in managing neuropathic pain when both formulations are administered according to the label instructions. (Trial Tr. (Brown), 878:10-13.)

593. Gralise addresses the drawback that immediate release gabapentin must be dosed three times a day to treat neuropathic pain, as Gralise need only be administered once daily with the evening meal. (Trial Tr. (Brown), 878:1-3, 882:1-4.)

594. Gralise addresses the unfavorable side effect profile of immediate release gabapentin when administered to treat neuropathic pain, because patients taking Gralise experience lower incidences of both somnolence and dizziness. (Trial Tr. (Brown), 878:6-9, 878:19-880:13; *compare* PTX000196 (DEPOACT0026320) *with* PTX000353 (DEPOACT0976447); *see also* PTX000266 (DEPOACT0872491).)

595. The fact that patients taking Gralise to treat neuropathic pain encounter fewer side effects than patients taking Neurontin, when both medications are administered according to label instructions, is reflected in the peer-reviewed literature (*e.g.*, PTX000266) and in a comparison of the product inserts. (*Compare* PTX000196 (DEPOACT0026320) *with* PTX000353 (DEPOACT0976447).)

596. Because there are no head-to-head studies comparing Neurontin and Gralise directly, a comparison of the clinical trial data in product inserts is the best alternative available to clinicians who want to compare the side effect profiles of Neurontin and Gralise. (Trial Tr. (Brown), 878:14-23.)

597. Neither Lyrica (pregabalin), Tapentadol, nor Cymbalta were available in October 2001. (Trial Tr. (Sinatra), 907:3-14.)

598. The incidences of dizziness and somnolence observed in the clinical trials summarized in the Neurontin and Gralise product inserts are as follows. (*Compare* PTX000196 (DEPOACT0026320) *with* PTX000353 (DEPOACT0976447).)

	Neurontin (PTX000196)		Gralise (PTX000353)	
	Placebo	Active Ingredient	Placebo	Active Ingredient
Dizziness	7.5%	28.0%	2.2%	10.9%
Somnolence	5.3%	21.4%	2.7%	4.5%

599. It was appropriate for Dr. Brown to conclude based on a comparison of the product inserts that patients taking Gralise for their neuropathic pain experienced fewer incidences of dizziness and somnolence than did those who took Neurontin to manage their neuropathic pain, despite differences in the placebo responses. (*See* Trial Tr. (Brown), 878:14-23 (testifying that in the absence of a head-to-head study, clinicians would compare, *inter alia*, product inserts).)

600. Dr. Sinatra provided no basis in fact to discount Dr. Brown's reliance on the clinical trials summarized in the product inserts for Gralise and Neurontin.

601. Dr. Sinatra did not dispute that clinicians frequently observe variability of placebo responses in pain management studies. (*See* Trial Tr. (Brown), 880:14-20.)

602. Dr. Sinatra did not dispute that no one understands why certain patients respond to the placebo. (*See* Trial Tr. (Brown), 881:18-20.)

603. Nor did Dr. Sinatra dispute that the most likely explanation for the variability in the placebo responses is the time of day participants took the placebo: three times a day in the Neurontin trials and only once a day with the evening meal in the Gralise trials. (*See* Trial Tr. (Brown), 880:14-882:9.)

604. Dr. Sinatra disagreed that the product inserts for Neurontin and Gralise can be compared to assess the likelihood of experiencing dizziness and somnolence. (Trial Tr. (Sinatra), 901:10-902:16.)

605. But Dr. Sinatra merely indicated that there are some differences in the clinical study designs that precluded comparing their incidences of side effects; he never explained how those differences in study designs could have contributed to the variability in incidences of the side effects of dizziness and somnolence. (Trial Tr. (Sinatra), 901:10-902:16.)

606. Dr. Sinatra's speculation is insufficient to discount Dr. Brown's testimony as to how a pain management physician would compare data contained in these two product inserts and that such a comparison shows that Gralise addresses the drawback of the side effects of dizziness and somnolence caused by Neurontin.

C. SOPHISTICATED COMPANIES FAILED IN THEIR ATTEMPTS TO MAKE AN EFFECTIVE EXTENDED RELEASE GABAPENTIN DOSAGE FORM

1. Warner-Lambert, the Maker of Blockbuster Immediate Release Gabapentin Drug Neurontin, Failed To Make an Effective Extended Release Gabapentin Formulation

607. Dr. Bockbrader testified that Warner-Lambert was unable to develop a controlled release dosage form of gabapentin and was skeptical of developing a controlled-release dosage form. (Trial Tr. (Bockbrader), 748:14-19.)

608. Warner-Lambert submitted the Neurontin NDA to the FDA in late 1992 and was approved in 1993 for add-on epilepsy indication. The label for Neurontin has since been expanded to include postherpetic neuralgia, which was approved in 2002. (Trial Tr. (Bockbrader), 749:10-19.)

609. Neurontin was selling over a billion dollars per year in the late 1990s. (Trial Tr. (Gidal), 865:5-12.)

610. Three types of Neurontin formulation are on the market: 100, 300 and 400 mg capsule formulations; 600 and 800 mg tablet formulations and 250 ml/5 ml liquid formulation. All of these formulations are immediate release gabapentin

dosages. They were originally marketed by Warner-Lambert Parke-Davis, but there are also generics out there now. (Trial Tr. (Bockbrader), 750:12-751:1.)

611. Neurontin is taken three times a day because of the short half-life of approximately six hours in the body. Rule of thumb was that anti-convulsant should be dosed close to its half-life to minimize peak and trough fluctuations within one dosing. (Trial Tr. (Bockbrader), 751:3-10.)

612. Warner-Lambert was interested in creating a form of gabapentin with reduced dosing frequency to improve patient compliance. (Trial Tr. (Bockbrader), 751:11-18.)

613. Warner-Lambert initially made a conventional controlled release dosage form of gabapentin before 1985, but it had unacceptable exposure, meaning the area under the curve was low and the absorption stopped after around three to four hours when the dosage form hit the colon. (Trial Tr. (Bockbrader), 752:8-17; 752:23-753:24.)

614. As set forth in the Review Notes to NDA 20-235 for Neurontin submitted by Warner-Lambert, Warner Lambert informed the FDA that it had evaluated a 600 mg sustained release gabapentin tablet in Study # 877-076, but the results "indicated unacceptable sustained release characteristic." (Trial Tr. (Bockbrader), 754:18-755:14; NDA 20-235 Review Notes at 17, (PTX00213) (DEPOACT0101212).)

615. A complete description of study No. 877-076 performed by Warner-Lambert from the NDA 20-235 review notes is given below:

> "SUSTAINED RELEASE FORMULATION (Study # 877-076):
>
> Sponsor evaluated a pilot formulation of 600 mg sustained release gabapentin tablet relative to 400 mg oral solution in healthy volunteers. Results indicated unacceptable sustained release characteristic. Further, rate and extent of gabapentin decreases as the drug moves lower in the GI tract (described above; study #945-35). Due to these reasons firm does not intend developing any sustained release formulations."

(NDA 20-235 Review Notes at 17, at DEPOACT0101212.)

616. The NDA 20-235 review further notes that the "rate and extent of gabapentin decreases as the drug moves lower in the GI tract," indicating that gabapentin absorption decreases as the dosage form moves down the gastrointestinal tract. (NDA 20-235 Review Notes at 17, (PTX000213), at DEPOACT0101212.)

[redacted] which tried to develop an extended release form of gabapentin from 1999 to 2001. [redacted]

[redacted] Andrx tried three different approaches: 400 mg color-coded gabapentin

extended-release (XT) tablets; 400 mg laser drilled gabapentin XT tablets, and 600 mg gabapentin extended release tablets.

(Trial Tr. (Felton), 1003:8-14; PTX000162 (ANDRXGAB0002059-2061); PTX000159 (ANDRXGAB0002038-2045).)

(PTX000149 (ANDRXGAB0000197).)

(PTX000149, PTX000162, PTX000159.)

(PTX000160 (ANDRXGAB0002383-2389); PTX000164 (ANDRXGAB0002050-2057).)

[redacted](PTX000165 (ANDRXGAB0002407); PTX000166 (ANDRXGAB0002417); PTX000167 (ANDRXGAB0002420-2510).)

[redacted]

(PTX000165; PTX000166; PTX000167.)

[redacted](PTX000155 (ANDRXGAB0001406); PTX000150 (ANDRXGAB0000235-259); PTX000153 (ANDRXGAB0001393-1404).)

[redacted]

(PTX000155; PTX000150; PTX000153.)

D. RATHER THAN SOLVE THE DIFFICULTIES IN MAKING AN EFFECTIVE CONTROLLED RELEASE GABAPENTIN FORMULATION, COMPANIES SOUGHT ALTERNATIVE SOLUTIONS

1. Warner-Lambert Focused on an Alternative to Gabapentin, Pregabalin, Which Did Not Have Gabapentin's Narrow Window and Saturable Absorption Drawbacks

627. From around 1996, Warner-Lambert started working on pregabalin. (Trial Tr. (Bockbrader), 760:12-19.)

628. Pregabalin is a different drug, but is in the same category as gabapentin. Unlike gabapentin, pregabalin displays linear absorption kinetics, which means if the amount of drug dose is doubled, the exposure to the drug is doubled. Further, bioavailability of pregabalin is greater than 90% at all doses studied, whereas bioavailability of gabapentin decreases with increasing dose. (Trial Tr. (Bockbrader), 760:12-761:11; 762:24-763:4.)

629. Additionally, the absorption window for pregabalin is twice as long as that of gabapentin, since pregabalin is also absorbed in the ascending colon. (Trial Tr. (Bockbrader), 763:12-23.)

630. Pregabalin is marketed as Lyrica by Warner-Lambert's successor Pfizer and was approved in 2005. (Trial Tr. (Bockbrader), 763:24-764:1.)

2. Xenoport Documented the Drawbacks of Gabapentin and Created a Gabapentin Prodrug

631. XenoPort, a small biopharmaceutics firm, documented in a 2004 publication the drawbacks of gabapentin including gabapentin's narrow window of

absorption, saturability, and variability in absorption and explained that Xenoport had embarked on a completely different pathway to try to solve the problem of gabapentin by coming up with a gabapentin prodrug, gabapentin enacarbil, that by-passes the gabapentin transporters and uses a different transporter to achieve linear, non-saturable absorption. (Trial Tr. (Gidal), 846:16-850:11; PTX000269.)

632. Xenoport documented the failure to make a controlled release version of gabapentin and recognized the unique challenges with gabapentin.

> "Attempts to develop a sustained release formulation of gabapentin to reduce the frequency of dosing have not been successful to date because the amino acid transporter for gabapentin is not found in sufficient levels in the large intestine."

(PTX000277 (DEPOACT0970277) (emphasis added); Trial Tr. (Gidal), 852:23-853:16.)

> To date, efforts to develop a sustained release formulation of gabapentin have failed, primarily due to the lack of significant absorption of the drug in the large intestine (Kriel et al., 1997)."

(PTX000269 (DEPOACT0958153) (emphasis added).)

633. Xenoport explained its approach and reasoning for formulating gabapentin encarbil or Gabapentin XP. Xenoport noted that poor and unpredictable absorption of gabapentin, including the inter-person variability, and the narrow window of absorption of gabapentin.

> "The absorption pathway for gabapentin in human intestine can be saturated at doses that are used to treat neuropathic pain. As a result, ***plasma levels of gabapentin are unpredictable*** and may not reach

> therapeutically useful levels in some patients (Gidal et al., 2000). . . . Several larger clinical studies have clearly demonstrated the lack of dose proportionality for oral gabapentin (Gidal et al., 1998; Neurontin Summary Basis of Approval, NDA 20-235, U.S. Food And Drug Administration). The large ***interpatient differences in plasma gabapentin exposure*** observed clinically are likely the result of highly variable intestinal expression of the gabapentin transporter between individuals and the narrow localization of the transporter in the small intestine. A subset of patients appears to have limited ability to absorb gabapentin, possibly due to a lower abundance of the transporter in their intestines. This phenomenon may contribute to the relatively high incidence of nonresponders to Neurontin therapy reported in clinical trials (Backonja et al., 1998; Rice and Maton, 2001).
>
> Following oral absorption, gabapentin is rapidly excreted in the urine with a half-life of approximately 5 to 7 h. As a result, gabapentin must be administered three or four times per day to maintain therapeutic levels. It has been shown that dosing regimens requiring three or four doses per day lead to significant noncompliance in epilepsy patients (Richter et al., 2003). ***To date, efforts to develop a sustained release formulation of gabapentin have failed, primarily due to the lack of significant absorption of the drug in the large intestine*** (Kriel et al., 1997)."

(PTX000269 at DEPOACT0958152-53 (emphasis added).)

634. In light of the drawbacks of gabapentin described above, Xenoport designed a drug that purportedly overcame such drawbacks.

> "XP13512 (Fig. 1) is a novel prodrug of gabapentin designed to overcome the pharmacokinetic limitations of gabapentin. The prodrug was engineered to be recognized as a substrate by two high-capacity nutrient transporters that are broadly distributed in the intestinal tract of humans."

(PTX000269 (DEPOACT0958153).)

3. Andrx Documented the Drawbacks of Neurontin and Made Gabapentin Prodrugs and Formulations Containing the Prodrugs

[redacted] (Trial Tr. (Felton), 1018:16-25.)

636. Andrx received a patent on prodrugs of gabapentin. (Trial Tr. (Felton), 1018:16-18.)

637. In that Patent, Andrx acknowledges the drawbacks of Neurontin, an immediate release dosage form of gabapentin, and a need for a once-a day gabapentin regimen.

> Gabapentin is a cyclohexaneacetic acid derivative that is sold under the trademark NEURONTIN® for the treatment of partial seizures in adults with epilepsy. The current administration regimen requires 900 to 1800 mgs/day and given in divided doses of three times per day using 300-400 mg capsules. While the drug is highly effective for its prescribed use, ***there is a need to develop a version of the drug that is administered in a once-a -day regimen and which provides an equally efficacious pharmaceutical product and improved side effect profile.***
>
> At the typical dosage range (300-600 mgs T.LD.) the oral bioavailability is approximately sixty percent. . . . Thus, there is a need for an improved product profile that increases bioavailability and provides for a once a day dosing regimen.

(U.S. Patent No. 6,683,112 assigned to Andrx entitled "Gabapentin Prodrugs and Formulations" (PTX000306), Col.1, ll. 8-28 (emphasis added).)

[redacted] (PTX000306)

E. SKILLED ARTISANS WERE SKEPTICAL ABOUT THE FEASIBILITY OF AN EXTENDED RELEASE GABAPENTIN FORMULATION

640. Two gabapentin experts, Dr. Bockbrader and Dr. Gidal testified that one of ordinary skill in the art were skeptical as of October 2001 about the feasibility of an effective extended release gabapentin formulation.

1. Warner-Lambert Was Skeptical About the Efficacy of a Controlled Release Dosage Form of Gabapentin

641. After the Neurontin NDA was approved in 1993, Warner-Lambert renewed its efforts to look at extended release gabapentin formulation. Warner-Lambert met with a French company that had a gastric retention dosage form that purportedly was retained even in the fasted state. However, a publication by Dr. Wilding in 1995 which tested this dosage form indicated that there was no evidence that the formulation would be retained in the absence of food. (Trial Tr. (Bockbrader), 756:14-757:9.)

642. Dr. Bockbrader testified that Warner-Lambert was skeptical of the approach offered by the French company. Dr. Bockbrader explained that the dosage form was expected to have a 10-hour absorption window when taken with a meal; however, this meant that there would only be elimination for the next 14 hours if the dosage form is taken once daily. Given that gabapentin has a 6-hour half-life, gabapentin concentration was expected to drop at least two-fold in those 14 hours. Dr. Bockbrader concluded that Warner-Lambert's skepticism with this type of formulation was that the Cmins were going to be at least half of that of IR and were concerned that the controlled release form would not have the same efficacy as the immediate release form. (Trial Tr. (Bockbrader), 757:10-759:6.)

643. In addition to the French company, Warner-Lambert also discussed GITS formulation with Alza. GITS formulation is not gastrically retained, but is taken with food. Here again, there was concern that the controlled release formulation would not be equally effective as the immediate release dosage form. (Trial Tr. (Bockbrader), 764:5-13.)

644. Dr. Bockbrader further testified that he was not aware in 1995 of other solutions to the problems of extended release dosing with gabapentin and Warner-Lambert did not continue developing a controlled release gabapentin. (Trial Tr. (Bockbrader), 760:5-11.)

2. Unpredictability in Gabapentin Absorption Casted Doubts on Creating an Effective Controlled Release Gabapentin Dosage Form

645. Depomed's expert Dr. Barry Gidal testified that he was skeptical that one could craft a controlled release formulation of gabapentin that would be therapeutically effective. (Trial Tr. (Gidal), 816:24-817:5.)

646. Dr. Gidal was admitted as an expert in gabapentin pharmacokinetics and pharmacodynamics. (Trial Tr. (Gidal), 815:14-816:2.)

647. Defendants did not proffer anyone as an expert in gabapentin.

648. Dr. Gidal explained that the pharmacokinetics of gabapentin was not straightforward, but was unpredictable. When a drug exhibits linear absorption, one can predict how much drug is going to get in when a dose of the drug is given. That is not true with saturable absorption, seen with gabapentin. Further, there was inter-person variability in the absorption of gabapentin. If a dose of gabapentin is given to everyone in the courtroom, one cannot predict the level of drug in blood in an individual. Furthermore, there were potential food effects on gabapentin absorption. Finally, the mechanism underlying all these variables is unknown. There is likely a genetic mechanism, but it is unclear. Dr. Gidal concluded that for all these reasons, he was skeptical that an effective controlled release gabapentin formulation could be crafted. (Trial Tr. (Gidal), 817:8–818:1.)

649. Dr. Gidal testified that others in the industry were also skeptical that an effective controlled release dosage form could be formulated, including Xenoport. (Trial Tr. (Gidal), 846:16-850:11; PTX000269.). As Dr. Gidal explained, "this group of scientists [at Xenoport] was also skeptical that you could create a gabapentin-sustained release so what they developed was this prodrug that used completely different transport systems for gabapentin, or for gabapentin enacarbil. They tried to solve the problem a different way, by creating this prodrug that didn't rely on a limited window of absorption." (Trial Tr. (Gidal), 851:5-852:3.)

a. The Variable Effect of Food on Gabapentin Absorption Raised Doubts on the Efficacy of a Dosage Form Dependent on Fed Stomach

650. Food has a variable effect on gabapentin absorption, as described below. As such, a skilled artisan would have been skeptical whether a gabapentin formulation that needed to be taken with food would be effective.

651. Studies from Dr. Gidal's laboratory and others have indicated that food has variable effect on gabapentin absorption. Because both gabapentin and certain amino acids are transported by the same transporter, System L, it was hypothesized that in the presence of a protein rich diet gabapentin would be absorbed less because the amino acids in the protein would compete with gabapentin for transport. (Trial Tr. (Gidal), 829:21-831:9.)

652. Unexpectedly, however, the presence of a protein rich diet enhanced the bioavailability of gabapentin. (Trial Tr. (Gidal), 831:10-24; PTX000276 (DEPOACT0970241).)

653. To further understand food effects, Dr. Gidal evaluated gabapentin absorption following a diet of Neurontin mixed with water, apple sauce, orange juice or chocolate pudding. (Trial Tr. (Gidal), 832:18-834:8; PTX000270 (DEPOACT0958992).) The data from the study suggested that food composition, particularly protein, could influence gabapentin absorption. (*Id*.)

654. In light of the variability in gabapentin in the presence of food, Dr. Gidal concluded that one of skill in the art would be skeptical that that a controlled release gabapentin formulation would work. As Dr. Gidal explained, the studies suggested that gabapentin absorption and ultimately pharmacokinetics and therapeutic efficacy would not be predictable, which was a concern with treating patients. (Trial Tr. (Gidal), 831:25–832:13; 834:3-8)

655. Indeed, the FDA noted the variable effect of food on gabapentin absorption and the surprising efficacy of Gralise. The FDA further stated that it would not have approved Gralise based only on pharmacokinetic and biopharmaceutic findings, without the benefit of clinical trial demonstrating efficacy. (Trial Tr. (Gidal), 839:13-840:25.)

> It is certainly possible that the fluctuation in systemic exposure and the fat-dependent variability of absorption could affect the efficacy of

> G-ER [Gralise]. If the approval of G-ER rested solely on pharmacokinetic and biopharmaceutic findings, these issues could preclude approval. However, an adequate and well-controlled clinical trial was conducted in patients with PHN in which efficacy was demonstrated. . . . Since G-ER did demonstrate efficacy in the clinical trial, where the fat content of the meals consumed with G-ER was not controlled, it appears that despite the fluctuations in systemic exposure and fat-dependent variability of absorption, G-ER was efficacious in the treatment of PHN in the clinical study population.

(PTX000265 (DEPOACT0816312).)

656. In sum, a skilled artisan would have been skeptical whether a gabapentin formulation that is dependent on food would work, for the type of food that is eaten may affect gabapentin absorption and could render the formulation ineffective.

b. Significant Inter-Person Variability in Gabapentin Absorption Counseled Against the Effectiveness of a Controlled Release Dosage Form

657. Studies conducted by Dr. Gidal and others indicated that there was significant variability in gabapentin absorption between persons. This variability was seen with patients (Trial Tr. (Gidal), 823:12-25; PTX000502) and normal subjects. (Trial Tr. (Gidal) 824:9- 15.)

658. The results of the study with normal subjects were published in 2000 in Inter- and Intra-subject variability in gabapentin absorption and absolute bioavailability, Gidal et al.., Epilepsy Research 40 (2000) 123-127 (PTX000275)

> The results of the present studies do highlight the point that the use of 'average' population kinetic data may be misleading in situations

> where substantial variability exists. In other words, although the average variabiilty of a 600 mg oral dose of gabapentin was 49%, individual subjects may vary greatly (5-74%). The clinical implication is that 'typical' or 'usual' doses are likely to result in quite different plasma concentration in individual patients. Indeed, similar observations were noted by Beydoun et al. in an efficacy trial of gabapentin monotherapy.

(PTX000275 (DEPOACT0970237).)

659. As Dr. Gidal noted, inter-person variability in absorption of gabapentin ranged from 5 to 74%.

660. Dr. Gidal concluded that the inter-subject variability in gabapentin absorption caused him to be skeptical that an extended release gabapentin dosage form that is consistently absorbed across a population could be made. (Trial Tr. (Gidal), 826:14-21; 827:18-22.)

c. Sensitivity of Gabapentin to Degradation in Stomach Acid Counseled Against a Gastrically Retained Dosage Form

661. Gabapentin degrades slowly into lactam as a function of pH, temperature and buffers which can accelerate some of this process. (Trial Tr. (Gidal), 856:1-3;PTX000290)

662. Lactam was considered to be a toxic product in 2001 and was to be avoided.

> The lactams display a certain toxicity and must, therefore, be avoided as far as possible. For example, gabapentin a toxicity (LD_{50}, mouse) of more than 8000 mg/kg, for the corresponding lactam (VI), a toxicity of 300 mg/kg. Consequently, these impurities and the

> potential formation of such decomposition products during storage of pharmaceutical compositions must be reduced to a minimum for reasons of safety.

Lactam-Free Amino Acids, U.S. Patent No. 6,054,482 col. 4 ll. 50-57 (filed Jan. 25, 1995) (issued Apr. 25, 2000), PTX000361.)

663. Gabapentin is a drug that was known to degrade in the presence of acid more quickly to a toxic lactam. (Trial Tr. (Felton), 971:22-972:19)

664. A drug that stays in the stomach for a long period would be a concern because of the concern that an acidic environment could facilitate the lactam formation. (Trial Tr. (Gidal), 856:7-14.)

F. GRALISE® IS COMMERCIALLY SUCCESSFUL

1. The Market for PHN Drugs Is Mature and Competitive

665. Dr. Sean Nicholson was qualified as an expert in the field of economics in healthcare. (Trial Tr. (Nicholson), 1064:5-7.)

666. The products that compete with Gralise include Neurontin, generic gabapentin, Lyrica, Horizant, Lidoderm, Cymbalta, Savella and Qutenza, which are drugs approved for PHN and related indications. (PTX00703 at slide 3; Trial Tr. (Nicholson), 1067:2-17.)

667. Neurontin and Lyrica are manufactured and marketed by Pfizer; Cymbalta is manufactured and marketed by Eli Lilly. (Trial Tr. (Nicholson), 1067:18-23.)

668. The number of drugs, the age of the drugs, and the presence of large manufacturers indicates that this is a mature, competitive market. (Trial Tr. (Nicholson), 1068:2-14.)

2. Since Its Launch, Gralise Has Experienced Sustained and Rapid Growth in Prescriptions, Sales and Market Share

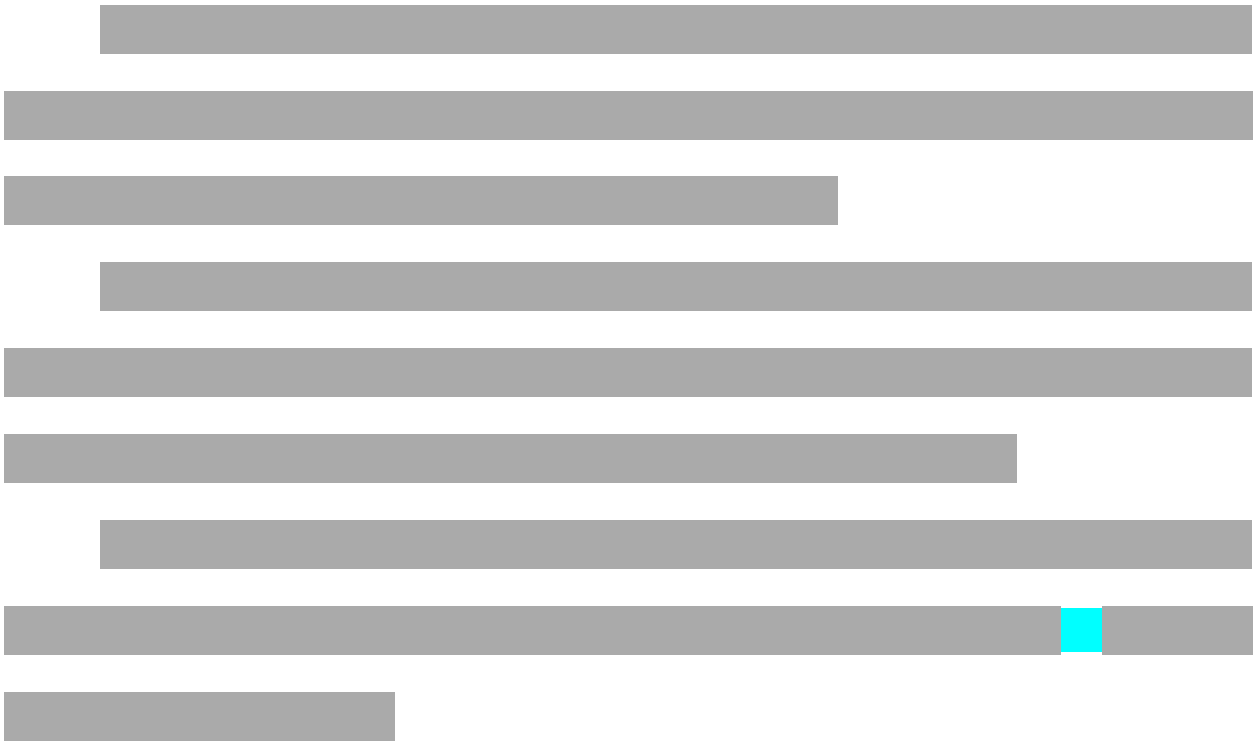
675. Among Gralise and competitor products, the share of extended units for Gralise increased year over year from launch in October 2011 through July 2013 (the most recent data available). (Trial Tr. (Sullivan), 1197:13-1199:2.)

676. The only other competitor product that increased its share of extended units in the same time frame was thrice-daily generic gabapentin. (Trial Tr. (Sullivan), 1199:13-1200:3.)

677. Thus, over this time period Gralise and generic gabapentin obtained market share at the expense of the other competitor drugs. (Trial Tr. (Sullivan), 1200:4-13.)

3. Net Present Value Analysis of Gralise Shows It Is Commercially Successful

678. Dr. Nicholson performed a net present value analysis using data including actual sales, royalty revenues, R&D and other costs, etc., which is the dominant way that businesses try to make decisions about whether to develop and invest in products. (Trial Tr. (Nicholson), 1071:6-21.)



682. Dr. Nicholson calculated the financial performance of Gralise starting in October 2011 through its first two years on the market, looking at revenues and costs of the product during this period. (Trial Tr. (Nicholson), 1073:7-23.)

683. To derive projected revenues and costs for Gralise after its first two years, Dr. Nicholson referred to industry average studies, and in particular, a study

by Mark Trusheim and colleagues that analyzed over 200 drugs launched in the U.S. between 1998 and 2008. (Trial Tr. (Nicholson), 1074:13 – 1075:11.)

684. Dr. Nicholson considers looking at the actual experiences of a large sample of pharmaceutical products on the market the best way to ensure the projections of Gralise are accurate and unbiased. (Trial Tr. (Nicholson), 1075:16 - 1076:6.)

685. The fact that Gralise is not yet profitable does not mean it is not commercially successful; pharmaceutical products requires substantial time and money to develop, and in fact, it takes, on average, 15-16 years for a pharmaceutical product to break even. (Trial Tr. (Nicholson), 1076:20 – 1077:20.)

686. This average time to profitability is based, in part, on a study by Henry Grabowski and colleagues, who analyzed a set of pharmaceutical products that were launched in the U.S. between 1980 and 1984, and charted the profitability of those products, whereupon Grabowski et al. found it took 16 years for those drugs, on average, to break even. (Trial Tr. (Nicholson), 1077:21 – 1078:3)

687. Grabowski later repeated this analysis for drugs launched between 1990 and 1994, and again found it took 15-16 years to break even. (Trial Tr. (Nicholson), 1078:4-7.)

690. Pharmaceutical firms frequently conduct net present value analyses as early as phase I studies, as they are deciding what projects to push forward; calculating net present value based in part on projected sales and costs is not speculation if it is based on careful analysis with accurate and unbiased forecasts. (Trial Tr. (Nicholson), 1089:22 – 1090-16.)

[redacted]

4. Gralise's Success Is Due to the Once-Daily Dosing Enabled by the Patents, Which Provides an Advantage Over Other Therapies

694. The success of Gralise is due to features of the product that are covered by the asserted patents; the key distinguishing feature of Gralise is that it can be taken once a day. (Trial Tr. (Nicholson), 1081:11 – 1082:7.)

695. Actavis has stipulated that Gralise practices the inventions recited in the asserted patent claims. ECF 328, p. 21 [Supp. Stip. Facts], ¶¶ 111-116.

696. The primary distinction between Gralise and other PHN therapies is the once daily dosing versus thrice daily. (Trial Tr. (Sullivan), 1191:11-22.)

697. Data from IMS Health shows that at or around the time of launch of Gralise in October of 2011, approximately 62 percent of the prescriptions that were

written for Gralise were for people who were switching from another therapy. (Trial Tr. (Sullivan), 1189:20-25.)

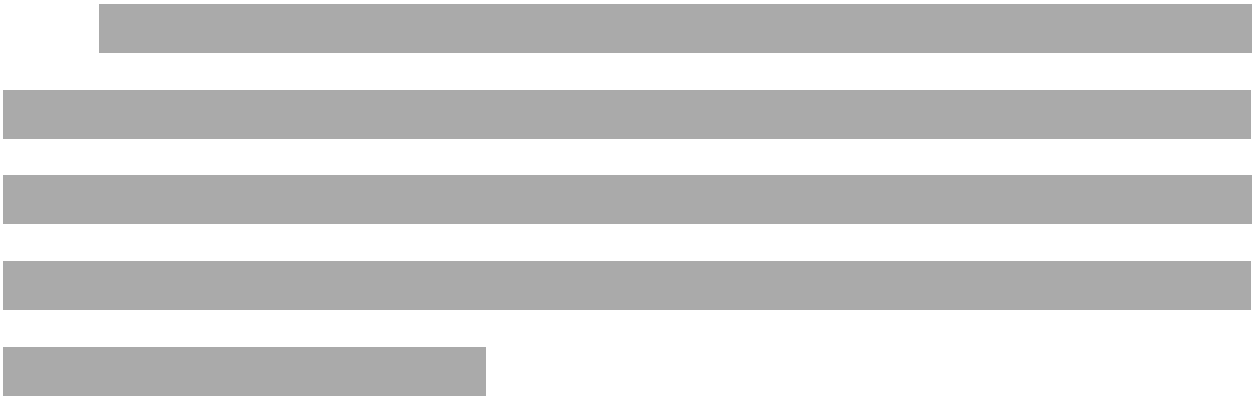
698. Data shows that as of January 2013, 15 months after Gralise was launched, three quarters of the patients who were taking Gralise had been taking a different PHN therapy before. (Trial Tr. (Nicholson), 1082:1-22; Trial Tr. (Sullivan), 1190:3-12.)

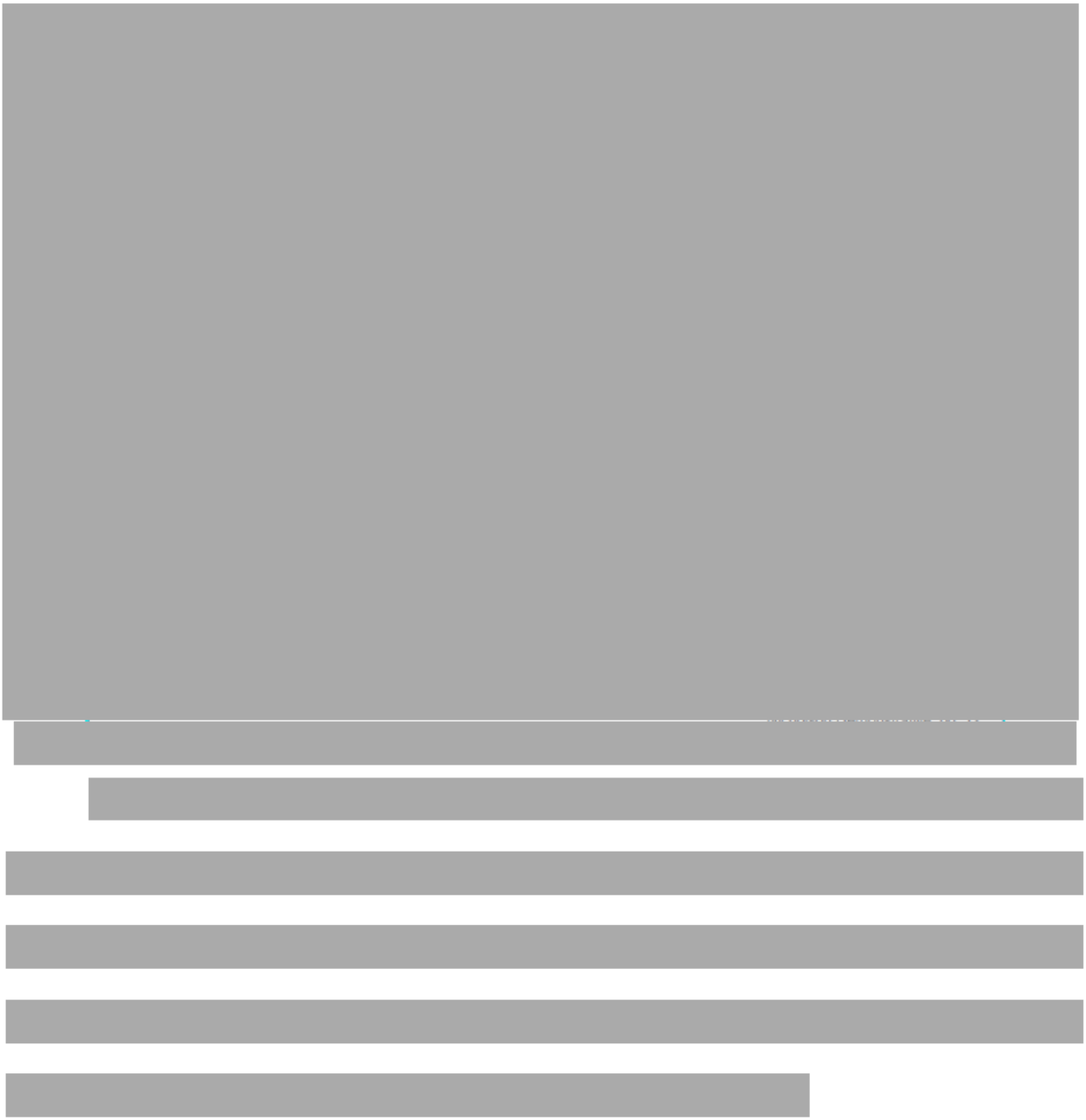
699. The fact that patients have to pay more for a product such as Gralise than a cheaper alternative, and they still switch to Gralise, is evidence that consumers are willing to pay for the patented features. (Trial Tr. (Nicholson), 1082:23 – 1083:5.)

700. By comparing marketing expenditures for Gralise with marketing expenditures of its competitors, among other things, Dr. Nicholson found that the success of Gralise is not due to excessive marketing efforts, because Depomed's marketing expenditures are in line with those of competitors. (Trial Tr. (Nicholson), 1084:3 – 1085:3; PTX000703, slide 11.)

5. Depomed's Licenses of Its Gastric Retention Technology to Others Evidences the Value of the Patents

701. The value of the asserted patents is further evidenced by the many licenses that other pharmaceutical companies have entered into with Depomed to license the gastric retention technology covered in the asserted patents. (Trial Tr. (Nicholson), 1085:12-21.)





704. These license agreements show that the licensees recognized the necessity and/or desirability to license the '280 and '962 patents in order to ensure freedom to undertake their own gastric retention development projects. (Trial Tr. (Sullivan), 1196:25 – 1197:7.)

705. Dr. Sullivan understands that any one infringed patent may put the infringer at risk of being precluded from selling a product that embodies that invention. (Trial Tr. (Sullivan), 1195:17-22; 1196:5-13.)

706. Licensees frequently take a license to particular patents to make sure they are clear to have freedom to operate. (Trial Tr. (Sullivan), 1196:25 – 1197:7.)

6. The Desire of Many Other Pharmaceutical Firms to Market a Generic Form of Gralise Further Evidences the Value of the Patents and Refutes Actavis' Contention That There is Little Market Demand for Gralise

707. Further evidence of value of the patented technology includes the behavior of the generic firms in filing their Abbreviated New Drug Applications, which shows the industry believes there is value in the technology covered by the patents. (Trial Tr. (Nicholson), 1085:6-21.)

708. Six entities filed ANDAs to manufacture and market a generic form of Gralise, including Actavis, Zydus, Incepta, Watson Laboratories, Par Pharmaceuticals and Impax Laboratories. ECF 001 – Case No. 3:12-cv-01358, DepoMed v. Actavis et al., [Original Complaint listing Actavis, Incepta and Watson Laboratories]; ECF 001 - Case No. 3:12-cv-02154, DepoMed v. Impax and Par, [Original Complaint listing Impax and Par]; ECF 001 - Case No. 3:12-cv-2813, DepoMed v. Zydus [Original Complaint listing Zydus]

709. It is reasonable to conclude that these six ANDA filers believed they could make a commercially successful product using substantially the same

technology as Gralise, which includes the asserted patents, as identified in the Orange Book for Gralise. (Trial Tr. (Sullivan), 1193:5-9; 1194:2-5; ECF 001 [Original Complaint listing Actavis, Incept and Watson Laboratories]; ECF 001 - Case No. 3:12-cv02154, DepoMed v. Impax and Par, [listing Impax and Par]; ECF 001 - Case No. 3:12-cv-2813, DepoMed v. Zydus [listing Zydus]; ECF 328, p. 3-5 [Supp. Stip. Facts], ¶¶ 7-12.)

710. According to Actavis' expert, Dr. Sullivan, it can be sensible and economically reasonable for a generic company or an ANDA filer to pursue a generic version of a branded drug because generic companies do not have to incur significant research and development costs, and do not have to spend as much on sales and marketing. (Trial Tr. (Sullivan), 1167:18-1168:8.)

7. Actavis Itself Went to Extraordinary Lengths to be the First ANDA Filer for a Generic Form of Gralise

711. Dr. Andrew Johnson is a Project Manager, or team leader, at Actavis, who testified at trial by videotaped deposition. (Trial Tr. (Johnson), 1139:6-10, 1141:6-12, 1142:2-5.)

[redacted]

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722. To develop a generic version of the Depomed Gralise® product, Actavis considered the Depomed patents and patent applications to derive the Gralise® formulation. (Trial Tr. (Hejazi), 52:1-20.)

723. Based on the Depomed patents and applications, Actavis designed an in-house reference that included hydroxypropylmethyl cellulose and polyethylene oxide, which represented Actavis' best understanding of the formulation of Gralise. (Trial Tr. (Hejazi), 53:10-19; PTX000014 (ACTGAB000000336).)

724. Actavis attempted to design its formulation for [redacted] (Trial Tr. (Hejazi), 57:12-15; 61:22–62:3; PTX000014 (ACTGAB000000336).)

725. In particular, Actavis used [redacted] (Trial Tr. (Hejazi), 61:14-18; PTX000014 (ACTGAB000000336).)

726. The Actavis ANDA product uses [redacted] (Trial Tr. (Hejazi), 58:8-20, 61:8-13.)

727. Both products use [redacted] (Trial Tr. (Hejazi), 61:4-7; PTX000014 (ACTGAB000000336).)

728. Actavis understood that [redacted] and observed that their [redacted] (Trial Tr. (Hejazi), 53:20-24; 56:19–57:7; PTX000039.)

729. Actavis also understood that tablets [redacted] (Trial Tr. (Hejazi), 72:10-19.)